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*In contaminated or potentially contaminated procedures (*e.g.,* vaginal or abdominal hysterectomy), and for patients in whom infection at the operative site would present serious risk (*e.g.,* coronary artery bypass graft [CABG] surgery).

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Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep. pneumoniae, Streptococcus* species (excluding enterococci), *Staph. aureus, H. influenzae, H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *E. coli, E. aerogenes, Proteus mirabilis* and *Serratia marcescens.*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus, Staph. epidermidis, Streptococcus* species (excluding enterococci), *E. cloacae, Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa.*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli, Proteus mirabilis, Proteus vulgaris, M. morganii* and *Klebsiella* species (including *K. pneumoniae*).

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae,* including both penicillinase and nonpenicillinase producing strains.

PELVIC INFLAMMATORY DISEASE caused by *N. gonorrhoeae.*

BACTERIAL SEPTICEMIA caused by *Staph. aureus, Strep. pneumoniae, E. coli, H. influenzae* and *K. pneumoniae.*

BONE AND JOINT INFECTIONS caused by *Staph. aureus, Strep. pneumoniae, Streptococcus* species (excluding enterococci), *E. coli, P. mirabilis, K. pneumoniae* and *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS caused by *E. coli* and *K. pneumoniae.*

MENINGITIS caused by *H. influenzae, N. meningitidis* and *Strep. pneumoniae.* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph. epidermidis* and *E. coli.*

SURGICAL PROPHYLAXIS: Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (*e.g.*, vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (*e.g.*, during coronary artery bypass surgery).

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery. When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure.

SUSCEPTIBILITY TESTING: Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, reported with nearly all antibacterial agents, including ceftriaxone, may range in severity from mild to life-threatening. Therefore, consider this diagnosis in patients who present with diarrhea subsequent to administration of antibacterial agents.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After establishing diagnosis of pseudomembranous colitis, initiate therapeutic measures. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consider management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug effective against *C. difficile.*

PRECAUTIONS: *GENERAL:* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.*, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

Rare cases reported of sonographic abnormalities seen in the gallbladder; patients may also have symptoms of gallbladder disease. These abnormalities, variously described as sludge, precipitations, echoes with shadows, may be misinterpreted as concretions. Chemical nature of sonographically-detected material not determined. Condition appears to be transient and reversible upon discontinuation of Rocephin and conservative management. Therefore, discontinue Rocephin if signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above develop.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

PREGNANCY: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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[illegible] Segment I (fertility and general reproduction) and Segment III [illegible] with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

NURSING MOTHERS: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section. *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Rocephin should not be administered to hyperbilirubinemic neonates, especially prematures.

ADVERSE REACTIONS: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration.

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESTINAL—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

HEPATIC—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

RENAL—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%).

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%).

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours.

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days; in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone; piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone; bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION).

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NOTE: Rocephin in the frozen state should not be stored above -20°C.

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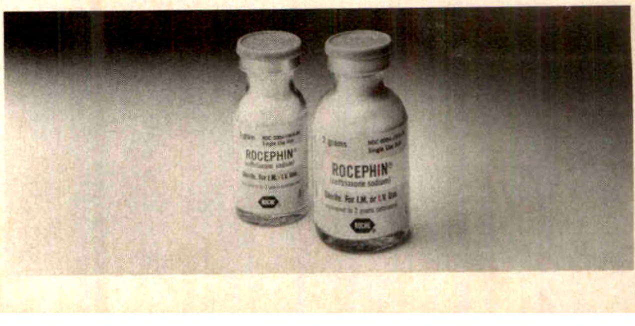

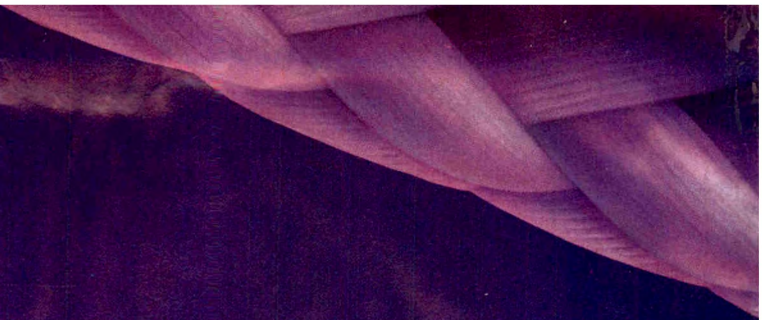

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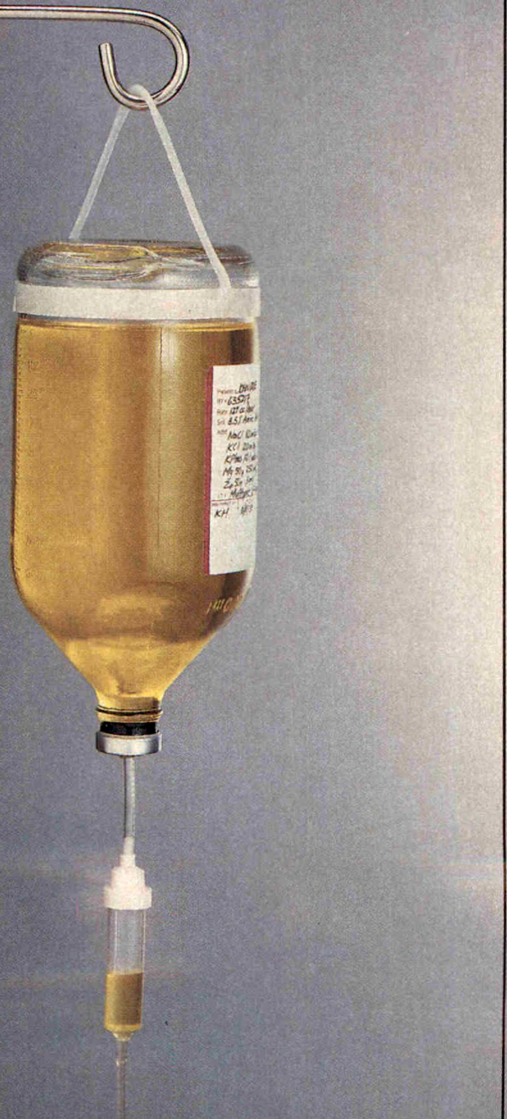

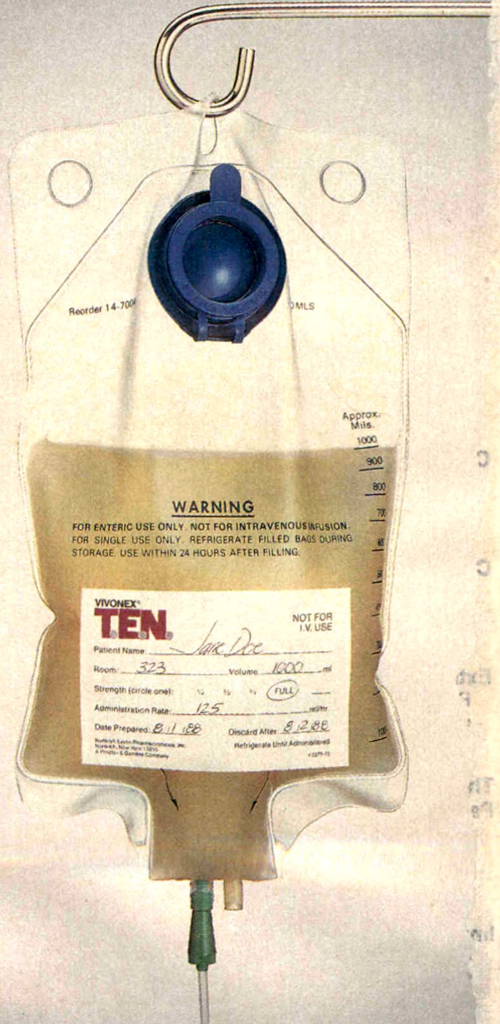
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References: 1. Andrassy RJ: Preserving the gut mucosal barrier and enhancing immune response. *Contemp Surg* 1988;32(2-A):21-27. **2.** Hoover HC Jr: Enteral elemental nutrition in major abdominal surgery. *Contemp Surg* 1986;28(4-A):12-17. **3.** Bower RH, Talamini MA, Sax HC, et al: Postoperative enteral vs parenteral nutrition: A randomized controlled trial. *Arch Surg* 1986; 121:1040-1045. **4.** Souba WW, Smith RJ, Wilmore DW: Glutamine metabolism by the intestinal tract. *JPEN* 1985;9:608-617. **5.** Fox AD, Kripke SA, Berman JR, et al: Reduction of the severity of enterocolitis by glutamine-supplemented enteral diets. *Surgical Forum* 1987;38:43-44. **6.** Hwang TL, O'Dwyer ST, Smith RJ: Preservation of small bowel mucosa using glutamine-enriched parenteral nutrition. *Surgical Forum* 1986;37:56-57.

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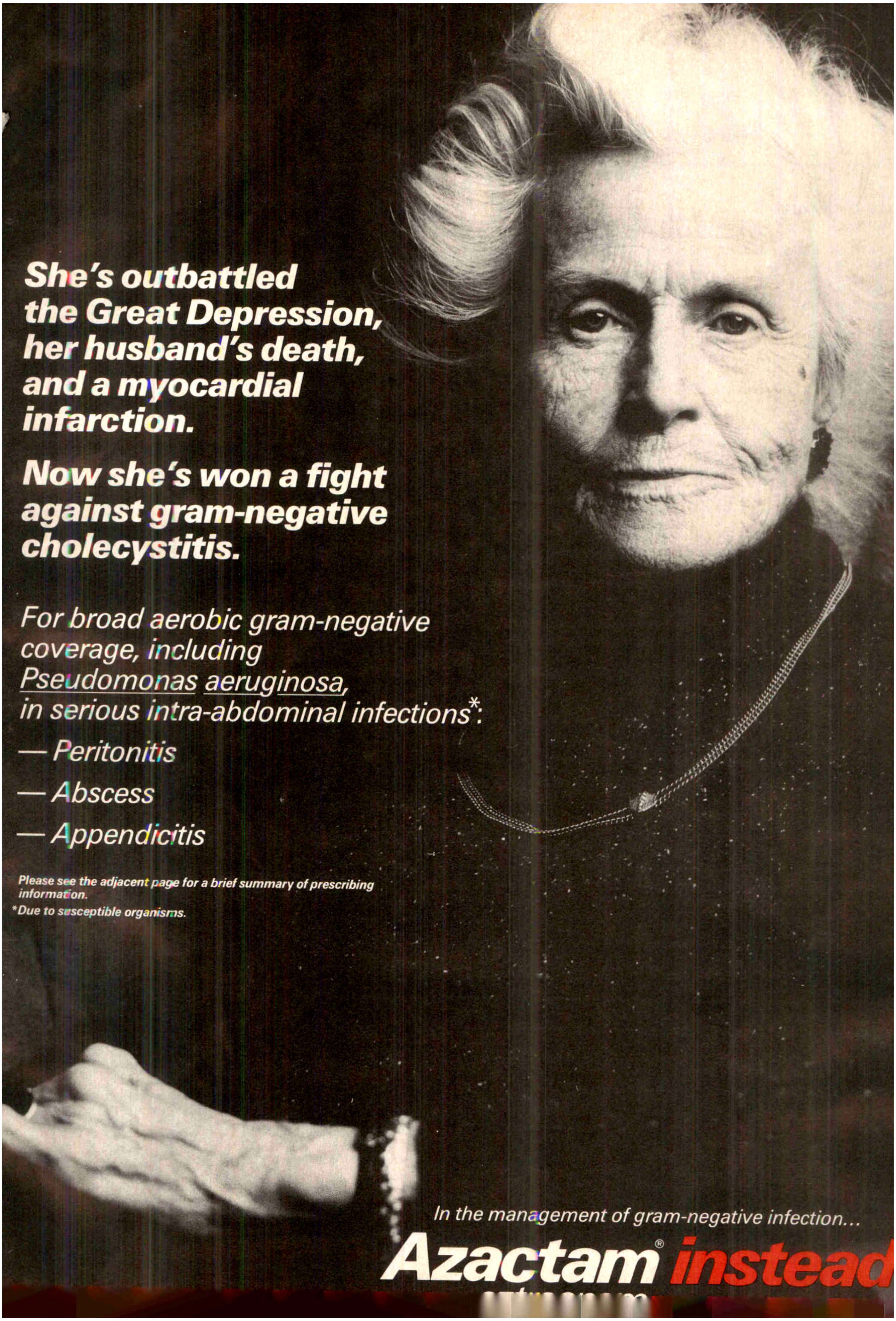
Joe A. Cates, MD; Ernst J. Drenick, MD; Mohammed Z. Abedin, PhD;
Jeff E. Doty, MD; Kimberly D. Saunders, MD; Joel J. Roslyn, MD, Los Angeles, Calif
- Revisional operations (MK) for failed bariatric surgical procedures warrant careful consideration; the potential for major complications and death should be considered against the proposed benefits.

REGULAR DEPARTMENTS

Calendar of Events 1237
Instructions for Authors . . . . **See Sept 1990 issue p 1225**
Classified Advertising 1405
Index to Advertisers 1242



She's outbattled the Great Depression, her husband's death, and a myocardial infarction.

Now she's won a fight against gram-negative cholecystitis.

For broad aerobic gram-negative coverage, including Pseudomonas aeruginosa, in serious intra-abdominal infections:*

- *Peritonitis*
- *Abscess*
- *Appendicitis*

Please see the adjacent page for a brief summary of prescribing information.

**Due to susceptible organisms.*

In the management of gram-negative infection...

Azactam® instead

In the management of gram-negative infection...

Azactam® instead.

aztreonam

AZACTAM® FOR INJECTION
Aztreonam For Injection

DESCRIPTION—AZACTAM (aztreonam, Squibb) is the first member of a new class of antibiotics classified as monobactams. AZACTAM is a totally synthetic bactericidal antibiotic with activity against a wide spectrum of gram-negative aerobic pathogens. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics.

AZACTAM For Injection is a sterile, nonpyrogenic, sodium-free, white to yellowish-white lyophilized cake, containing approximately 780 mg arginine per gram of aztreonam for intramuscular or intravenous use following constitution. Aqueous solutions of the product have a pH in the range of 4.5-7.5.

INDICATIONS AND USAGE—Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of the susceptibility testing are available; subsequently, appropriate antibiotic therapy should be continued.

AZACTAM For Injection is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: **Urinary Tract Infections** (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella oxytoca**, *Citrobacter* species* and *Serratia marcescens**. **Lower Respiratory Tract Infections,** including pneumonia and bronchitis caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae, Proteus mirabilis, Enterobacter* species and *Serratia marcescens**. **Septicemia** caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis**, *Serratia marcescens** and *Enterobacter* species. **Skin and Skin-Structure Infections,** including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli, Proteus mirabilis, Serratia marcescens, Enterobacter* species, *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Citrobacter* species*. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli, Klebsiella* species, including *K. pneumoniae, Enterobacter* species including *E. cloacae**, *Pseudomonas aeruginosa, Citrobacter* species* including *C. freundii** and *Serratia* species* including *S. marcescens**. **Gynecologic Infections,** including endometritis and pelvic cellulitis caused by *Escherichia coli, Klebsiella pneumoniae**, *Enterobacter* species* including *E. cloacae**, and *Proteus mirabilis**.

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

Concurrent Therapy—Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected, therapy should be initiated using an antianaerobic agent concurrently with AZACTAM. Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing, appropriate antibiotic therapy should be continued.

CONTRAINDICATION—Aztreonam is contraindicated in patients with known allergy to this antibiotic.

WARNINGS—Careful inquiry should be made for a history of hypersensitivity reaction to any antibiotic or other drugs. Antibiotics should be given with caution to any patient who has had some form of allergy, particularly to drugs. It is recommended that patients who have had immediate hypersensitivity reactions (e.g., anaphylactic or urticarial) to penicillins and/or cephalosporins should be followed with special care. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures.

PRECAUTIONS—General: In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy. If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenicity studies in animals have not been performed. Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level. Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

Pregnancy—Pregnancy Category B: Aztreonam crosses the placenta and enters the fetal circulation. Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Nursing Mothers—Aztreonam is excreted in breast milk in concentrations that are less than 1% of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

Pediatric Use—Safety and effectiveness have not been established in infants and children.

ADVERSE REACTIONS—Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9% and 2.4%, respectively. Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3% include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity: *Hypersensitivity*—anaphylaxis. *Hematologic*—pancytopenia, neutropenia, thrombocytopenia, anemia, leukocytosis, thrombocytosis. *Gastrointestinal*— abdominal cramps; rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. *Dermatologic*—purpura, erythema multiforme, urticaria, exfoliative dermatitis, petechiae, pruritus, diaphoresis. *Cardiovascular*—hypotension, transient ECG changes (ventricular bigeminy and PVC). *Respiratory*—one patient experienced flushing, chest pain, and dyspnea. *Hepatobiliary*—hepatitis, jaundice. *Nervous System*—seizure, confusion, vertigo, paresthesia, insomnia, dizziness. *Musculoskeletal*—muscular aches. *Special Senses*—tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing and nasal congestion, halitosis. *Other*—vaginal candidiasis, vaginitis, breast tenderness. *Body as a Whole*—weakness, headache, fever, malaise.

Adverse Laboratory Changes—Those reported without regard to drug relationship during clinical trials were: *Hepatic*—elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1% of recipients (see above). *Hemic*—increases in prothrombin and partial thromboplastin times, eosinophilia, positive Coombs test. *Renal*—increases in serum creatinine.

OVERDOSAGE—If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

DOSAGE AND ADMINISTRATION—Dosage adjustments are recommended for patients with impaired renal function. In elderly patients, estimates of creatinine clearance should be obtained and appropriate dosage modifications made if necessary.

HOW SUPPLIED—AZACTAM For Injection (Aztreonam For Injection)—Lyophilized—is supplied in single-dose 15 mL vials containing **500 mg,** or **1 g**/vial; in single-dose 30 mL vials containing **2 g**/vial; and in single-dose 100 mL intravenous infusion bottles containing **500 mg** or **1 g** or **2 g**/bottle.

Consult package insert before prescribing AZACTAM (aztreonam).

(J4-231A)

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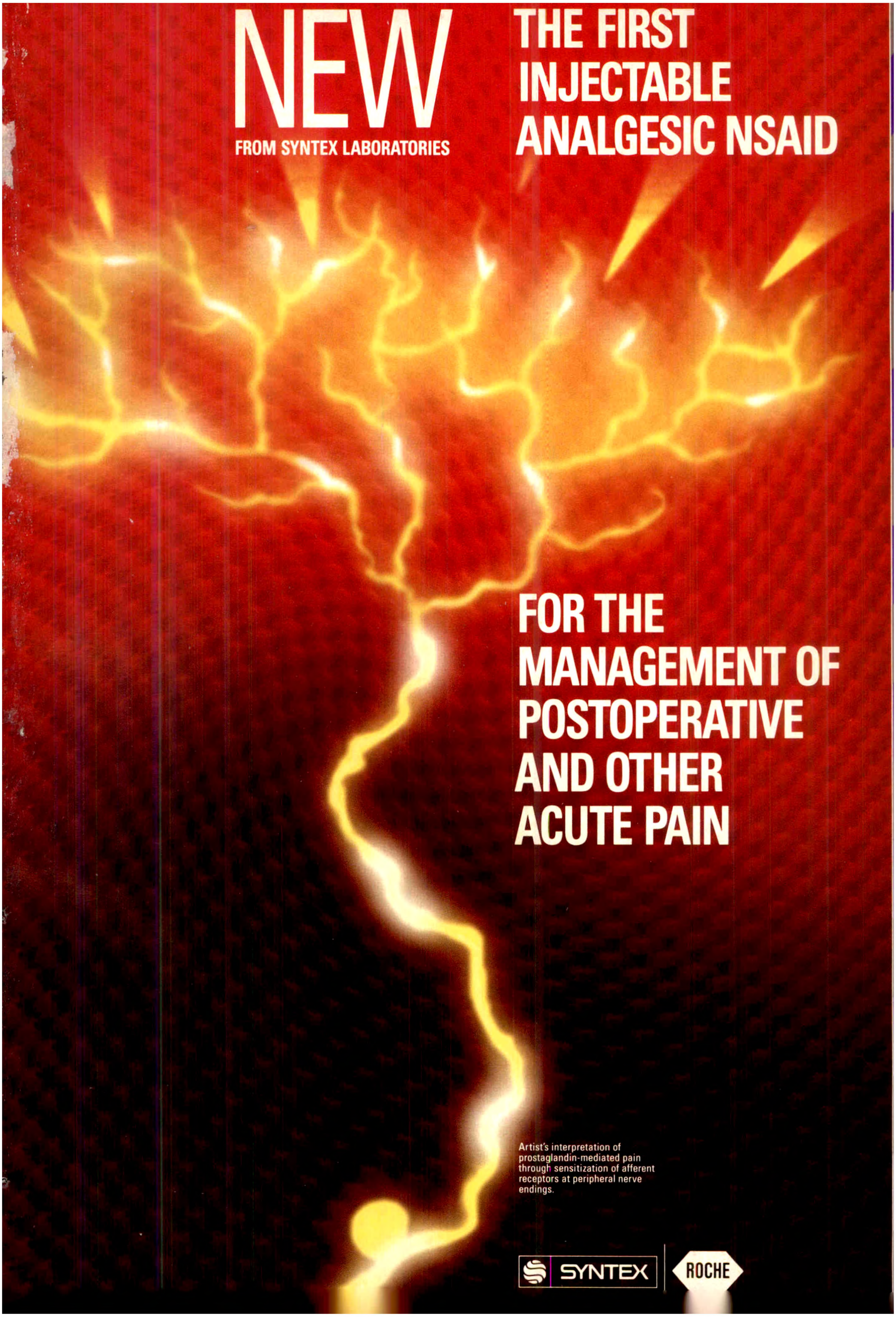
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

SQUIBB   *© 1990 E.R. Squibb & Sons, Inc., Princeton, NJ   680-502A   Issued: September 1990*



NEW

FROM SYNTEX LABORATORIES

THE FIRST INJECTABLE ANALGESIC NSAID

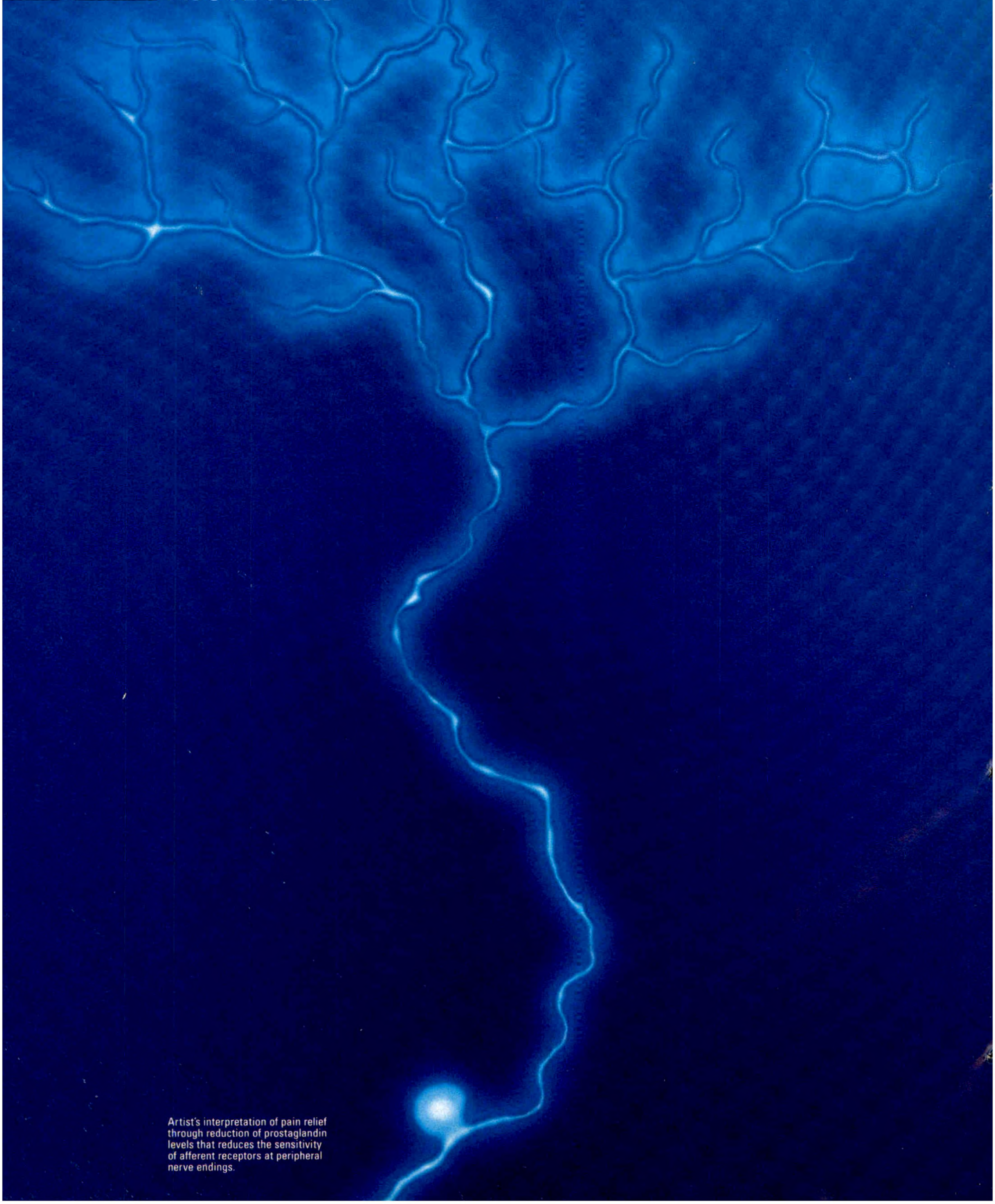
FOR THE MANAGEMENT OF POSTOPERATIVE AND OTHER ACUTE PAIN

Artist's interpretation of prostaglandin-mediated pain through sensitization of afferent receptors at peripheral nerve endings.

SYNTEX | ROCHE

FOR POSTOPERATIVE AND OTHER ACUTE PAIN

NEW



Artist's interpretation of pain relief through reduction of prostaglandin levels that reduces the sensitivity of afferent receptors at peripheral nerve endings.

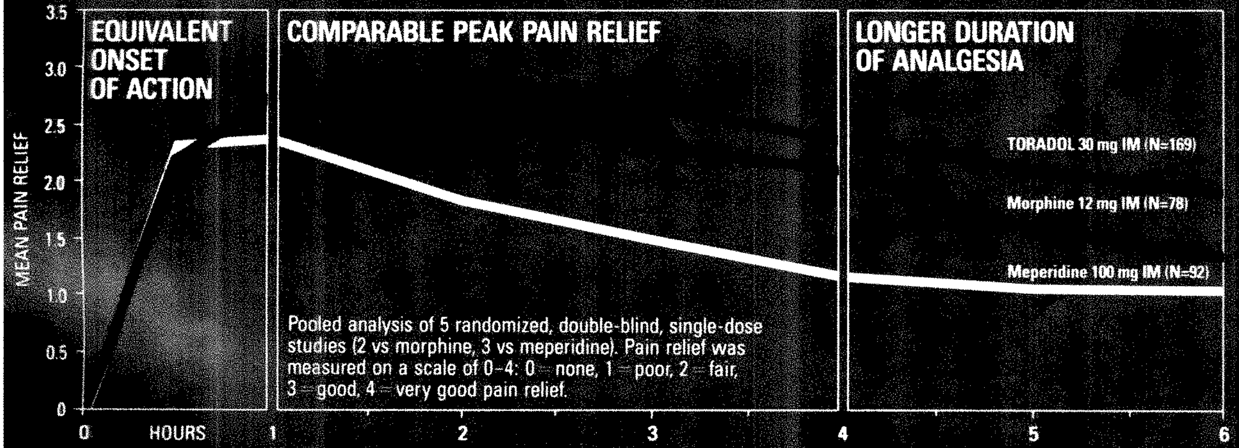
TORADOL® IM
INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

The first peripherally acting analgesic with efficacy comparable to morphine 12 mg and meperidine 100 mg

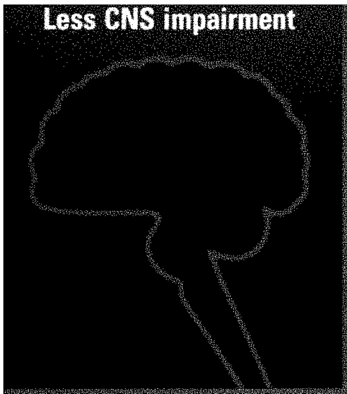
Analgesic efficacy of TORADOL IM administered 24–72 hours postsurgery[1]

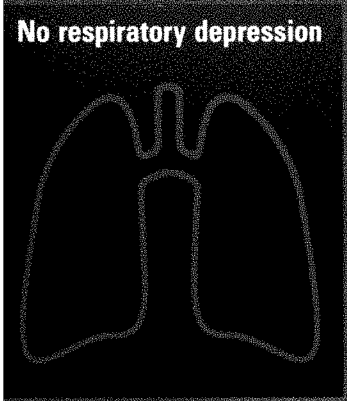


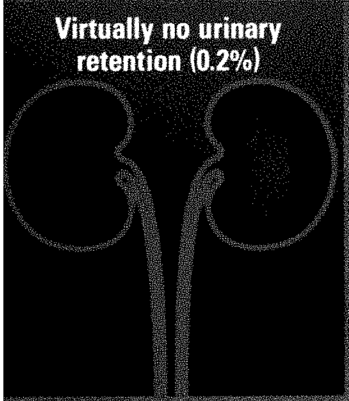
Pooled analysis of 5 randomized, double-blind, single-dose studies (2 vs morphine, 3 vs meperidine). Pain relief was measured on a scale of 0–4: 0 = none, 1 = poor, 2 = fair, 3 = good, 4 = very good pain relief.

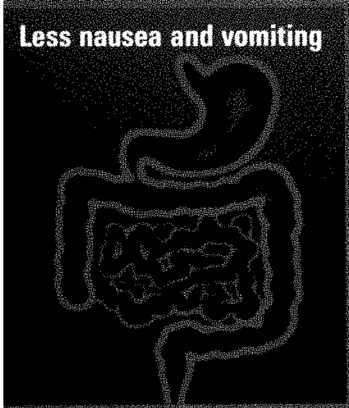
Documented efficacy following a broad range of surgical procedures:

General, orthopaedic, gynecologic (not for obstetric use)





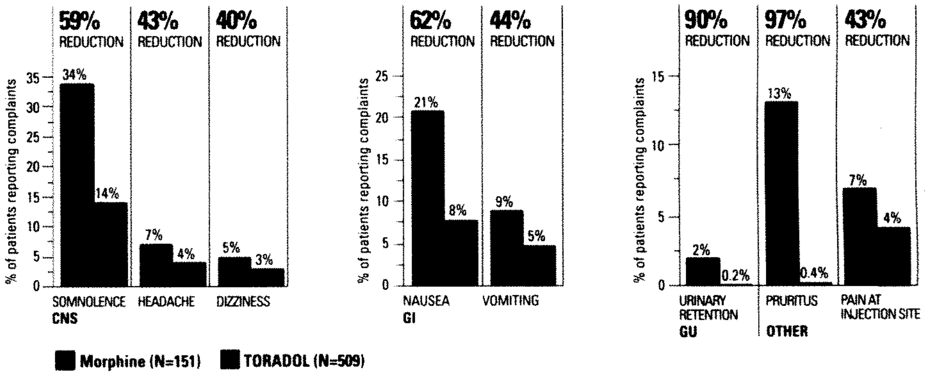




START RECUPERATION WITHOUT NARCOTIC SIDE EFFECTS[1]*

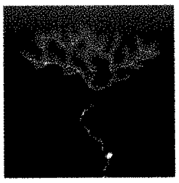
- 62% less nausea and 44% less vomiting
- 48% fewer CNS side effects
- No respiratory depression
- No hypotension
- 1-day earlier resumption of normal bowel function following major abdominal surgery
- No difference in clinically significant postoperative bleeding with TORADOL IM (0.4%) as compared to opiates (0.2%)

Comparison of most frequently reported side effects in 2 multi-dose studies (TORADOL IM vs morphine)**



Adverse reactions rates from short-term use of NSAIDs are generally from 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL IM.

**FOR
POSTOPERATIVE
AND OTHER
ACUTE PAIN**



NEW

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*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings," "Precautions," and "Adverse Reactions" sections of prescribing information.

**Most frequently reported side effects in major body systems with the exception of the cardiovascular system. 2% of patients treated with Toradol reported vasodilation as compared to 1% of patients treated with morphine.

1. Documented in 2 randomized, double-blind, multi-dose studies in which 509 patients received ketorolac 30 mg and 151 patients received morphine 10 mg or morphine 12 mg. Bowel function was evaluated in a subset of 47 patients undergoing gastric bypass surgery. Data on file, Syntex Laboratories, Inc., Document #90037-2.
2. Data on file, Syntex Laboratories, Inc., Document #90037-3

Please see brief summary of prescribing information on last page of this advertisement.

Analgesic therapy well suited for postoperative use

TORADOL IM is not an opiate

- Does not act on opiate receptor sites
- No potential for abuse
- No special restrictions or controls required

May be an appropriate alternative to narcotics for:

- Patients with narcotic allergy or intolerance
- Patients with a history of, or potential for, drug abuse or dependence

Special advantages may facilitate postoperative recuperation

- Patients with COPD or the obese–no negative effects on pulmonary function
- Ambulatory surgery patients–less CNS impairment (e.g., 59% less somnolence and 40% less dizziness)

Optimize analgesia on the day of surgery

- On the day of surgery, some TORADOL IM patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing
- On average, only one supplemental dose of narcotics may be required[2]

TORADOL® IM
INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

FOR POSTOPERATIVE AND OTHER ACUTE PAIN

NEW TORADOL® IM

INJECTIO

(KETOROLAC TROMETHAMINE) 15,3
60 M

OPTIMIZE ANALGESIC THERAPY FOR THE POSTOPERATIVE PATIENT

PROPER DOSAGE POSTOPERATIVELY

For maximum analgesia:

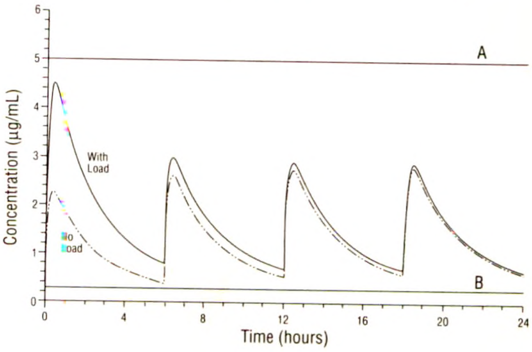
- Give patients prompt pain relief: start with loading dose of 60 mg IM
- Follow with maintenance dose of 30 mg IM Q6h to control pain
- The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter*

Simulated incremental plasma concentrations after 2 multi-dose regimens: (1) TORADOL IM 30 mg Q6h (no load); (2) TORADOL IM 60 mg LOADING DOSE followed by 30 mg Q6h

A = Plasma concentration above which side effects are more frequent

B = Estimated concentration required to obtain 50% decreases in pain intensity scores in dental surgery pain

Achieve optimal peak and trough plasma levels by starting with a loading dose (e.g., 60 mg), while maintaining plasma levels within the recommended therapeutic range. Follow with maintenance doses (e.g., 30 mg every 6 hours) to keep plasma levels in the optimal range.



Patient Selection: Use in patients with moderate-to-severe postoperative pain following general, orthopaedic, or gynecologic surgery (not for obstetric use)

Lower doses:

- Recommended for patients under 50 kg (110 pounds), patients over 65 years of age, and patients with reduced renal function
- Start with loading dose of 30 mg IM
- Follow with maintenance dose of 15 mg IM Q6h to control pain

On the day of surgery, some TORADOL IM patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing (not compatible in same syringe)

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*Dosages above those recommended are not associated with commensurate increases in efficacy.

Please see brief summary of prescribing information on last page of this advertisement.

© 1990 Syntex Laboratories, Inc. TD 90037

SYNTEX

ROCHE

TORADOL® IM (ketorolac tromethamine)

Brief Summary
TORADOL is a nonsteroidal anti-inflammatory drug (NSAID). TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP and 6.68 mg sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid. **Indications and Usage:** Indicated for the short-term management of pain. Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation. Not recommended for routine use with other NSAIDs because of the potential for additive side effects. TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam. Studies with other NSAIDs have not been done. Has been used concomitantly with morphine and meperidine without adverse interactions. **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. **Warnings:** Although TORADOL Injection is recommended for short-term use only, long-term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically. Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. High doses of an NSAID probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Impaired Renal or Hepatic Function: As with other NSAIDs, use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Renal Effects: As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow. In these patients, an NSAID may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly. Discontinuation of the NSAID is typically followed by recovery. Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema: These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions. Hepatic Effects: With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. These may progress, remain unchanged, or disappear with continued therapy. Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 1% of patients. Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction. Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24-48 hours after the drug is discontinued. In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates. **Drug Interactions:** TORADOL is highly bound to plasma protein (mean 99.2%), independent of concentration. In vitro binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5-10 μg/mL). TORADOL does not alter digoxin protein binding. At therapeutic concentrations of salicylate (300 μg/mL), in vitro binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels; hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding. In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected. In another study of 12 healthy volunteers, co-administration of heparin 5000 U s.c. and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time. There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration. This has not been studied with TORADOL. Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity. This has not been studied with TORADOL. TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity. Ketorolac was not mutagenic in tests with S. typhimurium, S. cerevisiae, or E. coli and did not cause chromosome breakage in the in vivo mouse micronucleus assay. Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively. **Pregnancy: Pregnancy Category B:** Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus. Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs. There are no adequate and well-controlled studies in pregnant women. TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available. **Labor and Delivery:** TORADOL is not recommended for use during labor and delivery. **Lactation and Nursing:** After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the corresponding values were 7.9 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman. **Pediatric Use:** TORADOL is not recommended for use in children. **Use in the Elderly:** Because ketorolac is cleared more slowly by elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly. **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL. In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn. Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days. **Incidence greater than 1%:** Body as a whole: edema. GI: nausea,* dyspepsia,* GI pain,* diarrhea. Nervous system: drowsiness,* dizziness, headache, sweating. Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine). *Incidence of reported reaction 3%-9%. Reactions occurring in less than 3% are unmarked. **Incidence 1% or less:** Body as a whole: asthenia, myalgia. Cardiovascular: vasodilation, pallor. Dermatologic: pruritus, urticaria. GI: constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting. Hemic and lymphatic: purpura. Nervous system: dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory: dyspnea, asthma. Special senses: abnormal taste, abnormal vision. Urogenital: increased urinary frequency, oliguria. **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist. Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing. Patients receiving TORADOL orally for ≥6 months have not developed tolerance and there is no pharmacologic basis to expect addiction. TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action. In vitro, TORADOL does not bind to opiate receptors. Thus, TORADOL does not have central opiate-like activity. **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses >100 mg/kg in rats, mice and monkeys symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed. **Dosage and Administration:** TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain. For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter. The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function. CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others.

Mfd. for Syntex Laboratories, Inc.
Palo Alto, CA 94304
by Survival Technology, Inc.
Bethesda, MD 20814

SYNTEX

02-2434-40-00 December 198

Calendar of Events

1990

October

American College of Surgeons, 1990 Clinical Congress, October 7-12, San Francisco, Calif.

November

The 11th World Congress of the Collegium Internationale Chirurgiae Digestivae (CICD), November 3-7, Convention Centre, Hotel Taj Palace Intercontinental, Sardar Patel Marg, New Delhi, India. Contact: Manohar J. Joshi, MS, FRCS(Eng), FACS, 1194/23 Ghole Rd, Pune-411005 India; (0212) 53698.

Western Surgical Association, November 11-14, Phoenix, Ariz.

Cleveland Clinic Foundation, "Colorectal Surgery," November 16-17, Bunts Auditorium, The Cleveland (Ohio) Clinic. Contact: The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Ave, TT31, Cleveland, OH 44195-5241; 444-5696 (local), or (800) 762-8173 (outside Ohio).

The 17th Annual Scientific Meeting of the Clinical Oncological Society of Australia, November 26-28, World Congress Centre, Melbourne, Australia. Contact: Secretary, Clinical Oncological Society of Australia, GPO Box 4708, Sydney, NSW 2001, Australia.

December

Southern Surgical Association, December 2-5, Boca Raton, Fla.

The Fourth International Symposium on Neutron Capture Therapy for Cancer, December 4-7, University of Sydney (Australia). This international symposium affords a unique opportunity for Australian cancer clinicians and researchers to bridge the information gap about recent developments in neutron capture therapy. Contact for details regarding air travel and preliminary program: Connections Plus Pty Ltd, 8 Richards Ave, Surry Hills, NSW 2010, Australia; 02 360 5711, 008 028210; FAX 02 360 5708.

1991

February

Pacific Coast Surgical Association, February 17-20, Pebble Beach, Calif.

Cleveland Clinic Foundation, "Colorectal Disease in 1991: An International Exchange of Medical and Surgical Concepts," February 14-16, The Westin Cypress Creek Hotel, Ft Lauderdale, Fla. Contact: The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Ave, TT31, Cleveland, OH 44195-5241; 444-5696 (local), or (800) 762-8173 (outside Ohio).

March

Central Surgical Association, March 7-9, Indianapolis, Ind.

American Association of Endocrine Surgeons, March 14-16, Baltimore, Md.

April

American Surgical Association, April 4-6, Boca Raton, Fla.

Southwestern Surgical Congress, April 21-24, Las Vegas, Nev.

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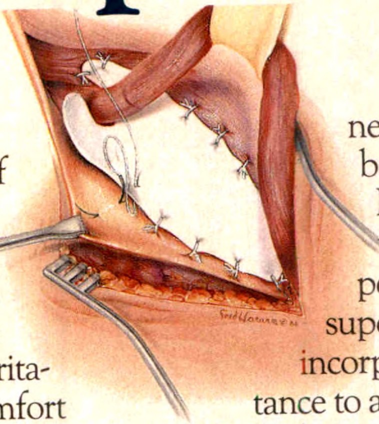

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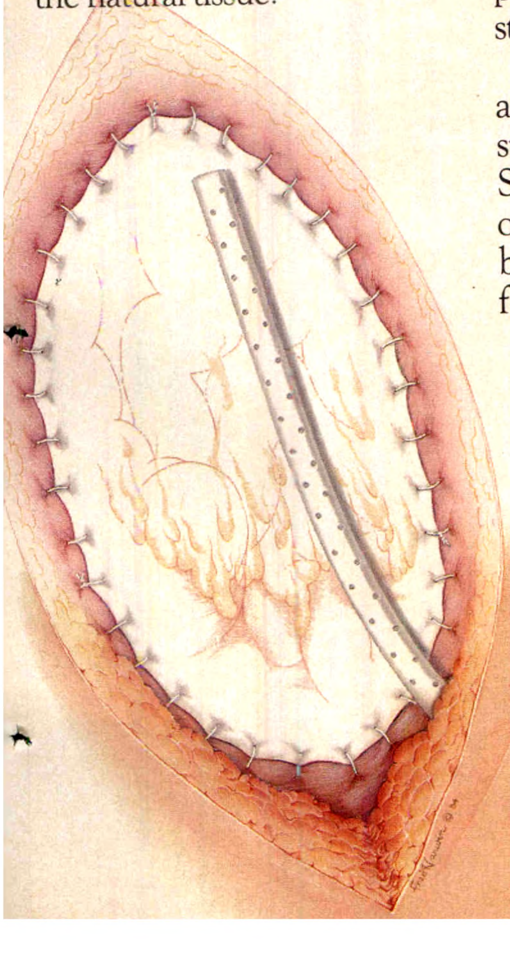

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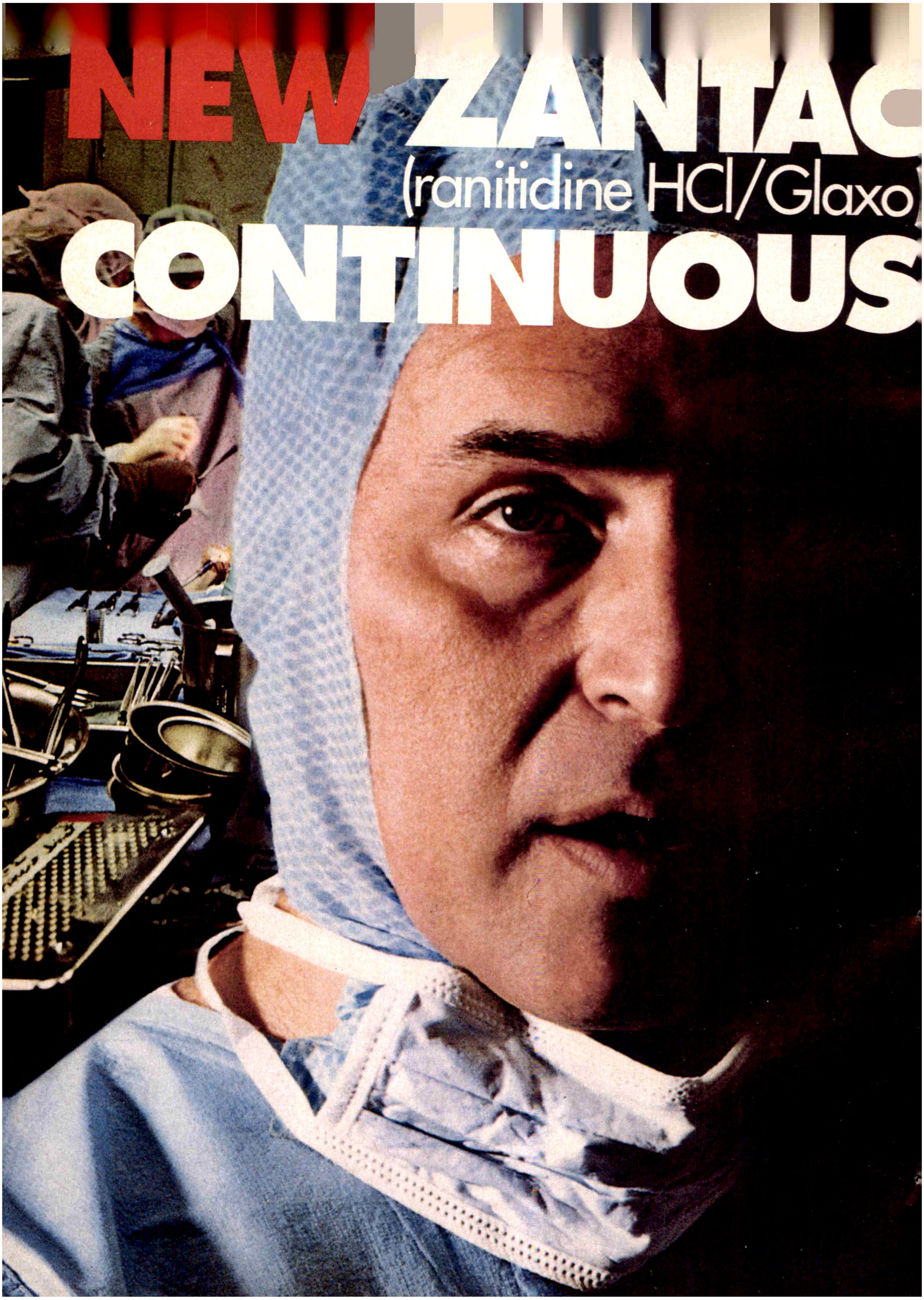
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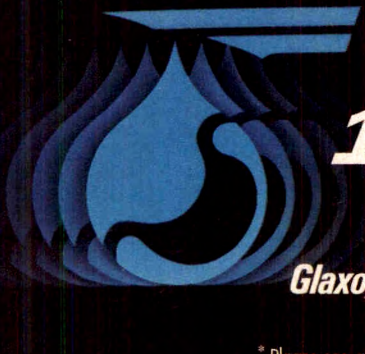

150 mg/day

Glaxo/ROCHE

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Research Triangle Park, NC 27709

* Please see complete Prescribing Information for indications.
† Rare cases of CNS effects, usually reversible, have been reported. Please see complete Prescribing Information for precautions.

Please see references and Brief Summary of Prescribing Information on next page.

on gastric pH and acid secretion: a comparison of relative efficacy and cost. *Ann Intern Med.* 1990;112(5):334-339. **2.** Data on file, Glaxo Inc. **3.** Sanders SW, Buchi KN, Moore JG, Bishop AL. Pharmacodynamics of intravenous ranitidine after bolus and continuous infusion in patients with healed duodenal ulcers. *Clin Pharmacol Ther.* 1989;46(5):545-551.

Zantac® Injection
(ranitidine hydrochloride)

BRIEF SUMMARY

Zantac® Injection Premixed
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® Injection/Zantac® Injection Premixed product labeling.
INDICATIONS AND USAGE: Zantac® Injection and Zantac® Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.
CONTRAINDICATIONS: Zantac® Injection and Zantac® Injection Premixed are contraindicated for patients known to have hypersensitivity to the drug.
PRECAUTIONS:
General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.
3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended doses for five days or longer. Therefore, it seems prudent in patients receiving intravenous (IV) ranitidine at doses greater than or equal to 100 mg qid for periods of five days or longer to monitor SGPT daily (from day 5) for the remainder of IV therapy.
4. Bradycardia in association with rapid administration of Zantac® Injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded (see DOSAGE AND ADMINISTRATION).
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.
Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at oral doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.
Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at oral doses up to 160 times the human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established.
Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) treated with oral Zantac were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.
ADVERSE REACTIONS: Transient pain at the site of intramuscular injection has been reported. Transient local burning or itching has been reported with IV administration of Zantac®.

The following have been reported as events in clinical trials or in the routine management of patients treated with oral or parenteral Zantac. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.
Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.
Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, asystole, atrioventricular block, and premature ventricular beats.
Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain, and rare reports of pancreatitis.
Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.
Musculoskeletal: Rare reports of arthralgias.
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia and aplastic anemia have been reported.
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.
Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.
OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.
DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® Injection/Zantac® Injection Premixed product labeling.)
Intramuscular Injection: 50 mg (2 ml) every six to eight hours. (No dilution necessary.)
Intermittent Intravenous Injection:

a. Intermittent Bolus: 50 mg (2 ml) every six to eight hours. Dilute Zantac Injection, 50 mg, in 0.9% Sodium Chloride or other compatible IV solution (see Stability) to a concentration no greater than 2.5 mg/ml (20 ml). Inject at a rate no greater than 4 ml per minute (five minutes).

b. Intermittent Infusion: 50 mg (2 ml) every six to eight hours. Dilute Zantac Injection, 50 mg, in 5% Dextrose Injection or other compatible IV solution to a concentration no greater than 0.5 mg/ml (100 ml). Infuse at a rate no greater than 5 to 7 ml per minute (15 to 20 minutes).

Zantac Injection Premixed solution, 50 mg, in 0.45% Sodium Chloride, 100 ml, requires no dilution and should be infused over 15 to 20 minutes.

In some patients it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of the dose, but generally should not exceed 400 mg per day.
Continuous Intravenous Infusion: Add Zantac Injection to 5% Dextrose Injection or other compatible IV solution. Deliver at a rate of 6.25 mg per hour (eg, 150 mg [6 ml] Zantac Injection in 250 ml of 5% Dextrose Injection at 10.7 ml per hour).

For Zollinger-Ellison patients, dilute Zantac Injection in 5% Dextrose Injection or other compatible intravenous solution to a concentration no greater than 2.5 mg/ml. Start the infusion at a rate of 1.0 mg/kg/h. If after four hours either a measured gastric acid output is greater than 10 mEq/h or the patient becomes symptomatic, the dose should be adjusted upwards in 0.5-mg/kg/h increments, and the acid output should be remeasured. Doses up to 2.5 mg/kg/h and infusion rates as high as 220 mg/h have been used.
Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 50 mg every 18 to 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.
HOW SUPPLIED: Zantac® Injection, 25 mg/ml, containing phenol 0.5% as preservative, is available as follows:
NDC 0173-0362-38 2-ml single-dose vials (Tray of 10)
NDC 0173-0363-39 10-ml multi-dose vials (Singles)
NDC 0173-0363-00 40-ml Pharmacy Bulk Packages (Singles)
NDC 0173-0362-00 2-ml single-dose, prefilled, disposable syringes (Singles)

Store below 30° C (86° F). Protect from light. Store 40-ml vial in carton until time of use.

Zantac® Injection Premixed in 0.45% Sodium Chloride, 0.5 mg/ml, is available as a sterile, premixed solution for IV administration in 100-ml, single-dose, flexible plastic containers (NDC 0173-0407-00). It contains no preservatives.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25° C); however, brief exposure up to 40° C does not adversely affect the product.

August 1990

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.

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NOW: REASON TO REFER VIRTUALLY EVERY PATIENT AFTER RESECTION OF DUKES' C COLON CANCER

PROVEN TO REDUCE RISK OF RECURRENCE 41%[1]

CP 24,995

In a 5½-year, cooperative, randomized trial of 929 Dukes' C patients after surgical resection:

ERGAMISOL® + 5-FU significantly increased overall survival and reduced tumor recurrences

Regimen well-tolerated; adverse reactions "did not greatly impede patients' compliance with their regimen"[1]

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LEVAMISOLE HCl TABLETS

in combination with 5-fluorouracil

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JANSSEN
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Reference: 1. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *New Engl J Med.* 1990;322:352-358.

Please see brief summary of prescribing information on next page.

ERGAMISOL® (Levamisole Hydrochloride) Tablets

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE: ERGAMISOL (levamisole hydrochloride) is only indicated as adjuvant treatment in combination with fluorouracil after surgical resection in patients with Dukes' stage C colon cancer.

CONTRAINDICATIONS: ERGAMISOL (levamisole hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or its components.

WARNINGS: ERGAMISOL (levamisole hydrochloride) has been associated with agranulocytosis, sometimes fatal. The onset of agranulocytosis is frequently accompanied by a flu-like syndrome (fever, chills, etc.); however, in a small number of patients it is asymptomatic. A flu-like syndrome may also occur in the absence of agranulocytosis. It is essential that appropriate hematological monitoring be done routinely during therapy with ERGAMISOL and fluorouracil. Neutropenia is usually reversible following discontinuation of therapy. Patients should be instructed to report immediately any flu-like symptoms.

Higher than recommended doses of ERGAMISOL may be associated with an increased incidence of agranulocytosis, so the recommended dose should not be exceeded.

The combination of ERGAMISOL and fluorouracil has been associated with frequent neutropenia, anemia and thrombocytopenia.

PRECAUTIONS: Before beginning this combination adjuvant treatment, the physician should become familiar with the labeling for fluorouracil.

Information for Patients: The patient should be informed that if flu-like symptoms or malaise occurs, the physician should be notified immediately.

Drug Interactions: ERGAMISOL (levamisole hydrochloride) has been reported to produce "ANTABUSE®"-like side effects when given concomitantly with alcohol. Concomitant administration of phenytoin and ERGAMISOL plus fluorouracil has led to increased plasma levels of phenytoin. The physician is advised to monitor plasma levels of phenytoin and to decrease the dose if necessary.

Laboratory Tests: On the first day of therapy with ERGAMISOL/fluorouracil, patients should have a CBC with differential and platelets, electrolytes and liver function tests performed. Thereafter, a CBC with differential and platelets should be performed weekly prior to each treatment with fluorouracil with electrolytes and liver function tests performed every 3 months for a total of one year. Dosage modifications should be instituted as follows: If WBC is 2500-3500/mm^3 defer the fluorouracil dose until WBC is > 3500/mm^3. If WBC is < 2500/mm^3, defer the fluorouracil dose until WBC is > 3500/mm^3; then resume the fluorouracil dose reduced by 20%. If WBC remains < 2500/mm^3 for over 10 days despite deferring fluorouracil, discontinue administration of ERGAMISOL. Both drugs should be deferred unless enough platelets are present (≥ 100,000/mm^3).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate animal carcinogenicity studies have not been conducted with levamisole. Studies of levamisole administered in drinking water at 5, 20, and 80 mg/kg/day to mice for up to 18 months or administered to rats in the diet at 5, 20, and 80 mg/kg/day for 24 months showed no evidence of neoplastic effects. These studies were not conducted at the maximum tolerated dose, therefore the animals may not have been exposed to a reasonable drug challenge. No mutagenic effects were demonstrated in dominant lethal studies in male and female mice, in an Ames test, and in a study to detect chromosomal aberrations in cultured peripheral human lymphocytes.

Adverse effects were not observed on male or female fertility when levamisole was administered to rats in the diet at doses of 2.5, 10, 40, and 160 mg/kg. In a rat gavage study at doses of 20, 60, and 180 mg/kg, the copulation period was increased, the duration of pregnancy was slightly increased, and fertility, pup viability and weight, lactation index, and number of fetuses were decreased at 60 mg/kg. No negative reproductive effects were present when the offspring were allowed to mate and litter.

Pregnancy: Pregnancy Category C: Teratogenicity studies have been performed in rats and rabbits at oral doses up to 180 mg/kg. Fetal malformations were not observed. In rats, embryotoxicity was present at 160 mg/kg and in rabbits, significant embryotoxicity was observed at 180 mg/kg. There are no adequate and well-controlled studies in pregnant women and ERGAMISOL should not be administered unless the potential benefits outweigh the risks. Women taking the combination of ERGAMISOL and fluorouracil should be advised not to become pregnant.

Nursing Mothers: It is not known whether ERGAMISOL is excreted in human milk; it is excreted in cows' milk. Because of the potential for serious adverse reactions in nursing infants from ERGAMISOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ERGAMISOL in children have not been established.

ADVERSE REACTIONS: Almost all patients receiving ERGAMISOL (levamisole hydrochloride) and fluorouracil reported adverse experiences. Tabulated below is the incidence of adverse experiences that occurred in at least 1% of patients enrolled in two clinical trials who were adjuvantly treated with either ERGAMISOL or ERGAMISOL plus fluorouracil following colon surgery. In the larger clinical trial, 66 of 463 patients (14%) discontinued the combination of ERGAMISOL plus fluorouracil because of adverse reactions. Forty-three of these patients (9%) developed isolated or a combination of gastrointestinal toxicities (e.g. nausea, vomiting, diarrhea, stomatitis and anorexia). Ten patients developed rash and/or pruritus. Five patients discontinued therapy because of flu-like symptoms or fever with chills; ten patients developed central nervous system symptoms such as dizziness, ataxia, depression, confusion, memory loss, weakness, inability to concentrate, and headache; two patients developed reversible neutropenia and sepsis; one patient because of thrombocytopenia; one patient because of hyperbilirubinemia. One patient in the ERGAMISOL plus fluorouracil group developed agranulocytosis and sepsis and died.

In the ERGAMISOL alone arm of the trial, 15 of 310 patients (4.8%) discontinued therapy because of adverse experiences. Six of these (2%) discontinued because of rash, six because of arthralgia/myalgia, and one each for fever and neutropenia, urinary infection, and cough.

For medical questions, call 1-800-253-3682 (9 AM-5 PM Eastern Time).

Adverse experience	ERGAMISOL N = 440 %	ERGAMISOL plus fluorouracil N = 599 %
Gastrointestinal		
Nausea	22	65
Diarrhea	13	52
Stomatitis	3	39
Vomiting	6	20
Anorexia	2	6
Abdominal pain	2	5
Constipation	2	3
Flatulence	<1	2
Dyspepsia	<1	1
Hematological		
Leukopenia		
<2000/mm^3	<1	1
≥2000 to <4000/mm^3	4	19
≥4000/mm^3	2	33
unscored category	0	<1
Thrombocytopenia		
<50,000/mm^3	0	0
≥50,000 to <130,000/mm^3	1	8
≥130,000/mm^3	1	10
Anemia	0	6
Granulocytopenia	<1	2
Epistaxis	0	1
Skin and Appendages		
Dermatitis	8	23
Alopecia	3	22
Pruritus	1	2
Skin discoloration	0	2
Urticaria	<1	0
Body as a Whole		
Fatigue	6	11
Fever	3	5
Rigors	3	5
Chest pain	<1	1
Edema	1	1
Resistance Mechanisms		
Infection	5	12
Special Senses		
Taste Perversion	8	8
Altered sense of smell	1	1
Musculoskeletal System		
Arthralgia	5	4
Myalgia	3	2
Central and peripheral nervous system		
Dizziness	3	4
Headache	3	4
Paresthesia	2	3
Ataxia	0	2
Psychiatric		
Somnolence	3	2
Depression	1	2
Nervousness	1	2
Insomnia	1	1
Anxiety	1	1
Forgetfulness	0	1
Vision		
Abnormal tearing	0	4
Blurred vision	1	2
Conjunctivitis	<1	2
Liver and biliary system		
Hyperbilirubinemia	<1	1

In worldwide experience with ERGAMISOL, less frequent adverse experiences included exfoliative dermatitis, periorbital edema, vaginal bleeding, anaphylaxis, confusion, convulsions, hallucinations, impaired concentration, renal failure, elevated serum creatinine, and increased alkaline phosphatase. An encephalopathy - like syndrome has been reported in patients treated with ERGAMISOL.

The following additional adverse experiences have been reported for fluorouracil alone: esophagopharyngitis, pancytopenia, myocardial ischemia, angina, gastrointestinal ulceration and bleeding, anaphylaxis and generalized allergic reactions, acute cerebellar syndrome, nystagmus, dry skin, fissuring, photosensitivity, lacrimal duct stenosis, photophobia, euphoria, thrombophlebitis, and nail changes.

HOW SUPPLIED: ERGAMISOL (levamisole hydrochloride) is available in white, coated tablets containing the equivalent of 50 mg of levamisole base, debossed "JANSSEN" and "L"
"50."

They are supplied in blister packages of 36 tablets (NDC 50458-270-36).

Store at room temperature, 15°-30°C (59°-86°F). Protect from moisture.

IN DUKES' C COLON CANCER

50 mg

ERGAMISOL®
LEVAMISOLE HCl TABLETS
in combination with 5-fluorouracil

Manufactured by:
Janssen Pharmaceutica, nv
Beerse, Belgium

Distributed by:
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JANSSEN
PHARMACEUTICA

Edition June, 1990   7500100-M   U.S. Patent Number 4,584,305

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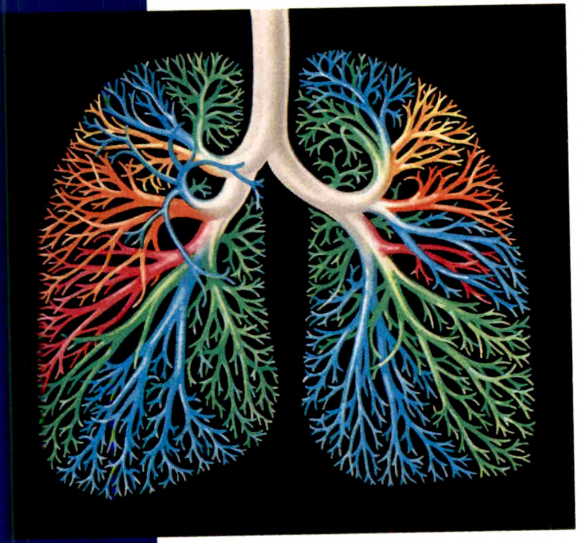
August 1990   JPI-ER-010

THE RESPIRATORY SEASON MEANS



TOUGH PATIENTS, TOUGH PATHOGENS...

ves 96% favorable clinical response (resolution + improvement) of
ons due to susceptible strains of indicated pathogens. See indi-
organisms in prescribing information.

activity does not necessarily imply a correlation with in vivo results.

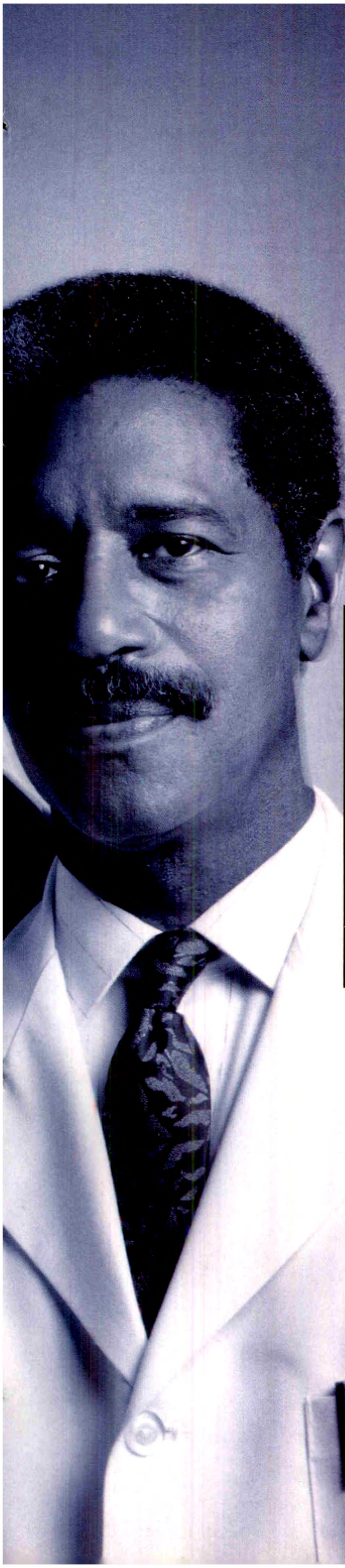
Concurrent administration of ciprofloxacin with theophylline may lead
ated plasma concentrations of theophylline and prolongation of its
ation half-life. This may result in increased risk of theophylline-related
e reactions. If concomitant use cannot be avoided, plasma levels of
ylline should be monitored and dosage adjustments made as
riate.

Antacids containing magnesium hydroxide or aluminum hydroxide interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

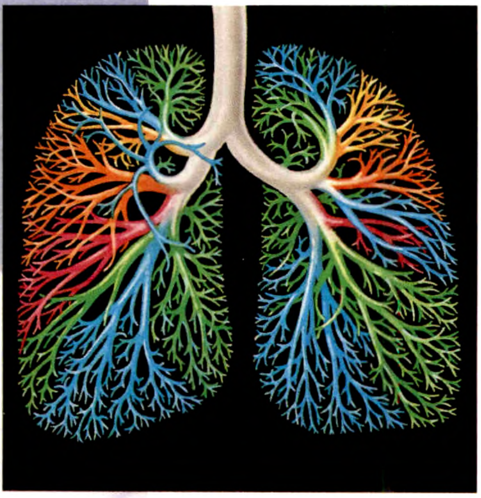
CIPRO® SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN.

See last page for brief summary of prescribing information.



IN LOWER RESPIRATORY INFECTIONS

CIPRO® MAKES A TOUGH THERAPEUTIC CHOICE EASIER.



Treating patients with lower respiratory infections is often a challenge.

These patients may smoke or drink excessively, or have underlying conditions such as COPD.

They could be elderly or immunocompromised or live in nursing homes where they are constantly exposed to multiple organisms.

Too often, they may have a history of repeated antibiotic use that has proven ineffective against their lower respiratory infections.

So, how do you manage these tough patients during the respiratory season?

By prescribing the "tough" agent that achieved **96%** clinical success in pneumonia, bronchitis, and bronchiectasis.[1*]

By prescribing Cipro®.

Cipro® TABLETS

(ciprofloxacin HCl/Miles)

The most potent fluoroquinolone.[2-4†]

Cipro® TABLETS
iprofloxacin HCl/Miles)

IN LOWER RESPIRATORY INFECTIONS

CIPRO® MAKES A TOUGH THERAPEUTIC CHOICE EASIER.

CIPRO® TABLETS
(ciprofloxacin HCl/Miles)

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

o® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in conditions listed below:

er Respiratory Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus abilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* and *Streptococcus umoniae.*

n and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, teus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas ginosa, Staphylococcus aureus, Staphylococcus epidermidis,* and *Streptococcus pyogenes.*

e and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens,* and *Pseudomonas aeruginosa.*

nary Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, udomonas aeruginosa, Staphylococcus epidermidis,* and *Streptococcus faecalis.*

ctious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni, Shigella flexneri,** *Shigella sonnei** when antibacterial therapy is indicated.

icacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS

istory of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other olones may also contraindicate the use of ciprofloxacin.

WARNINGS

ROFLOXACIN SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN. The oral admin- ation of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing ts of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and floxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature mals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

eral: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may to tremor, restlessness, lightheadedness, confusion, and rarely to hallucinations or convulsive seizures. There- , ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe ebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

naphylactic reactions following the first dose have been reported in patients receiving therapy with quinolones. ne reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial ma, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reaction. Anaphylactic tions may require epinephrine and other emergency measures. Ciprofloxacin should be discontinued at the first of hypersensitivity or allergy.

evere hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with outcome have been reported rarely (less than one per million prescriptions) in patients receiving ciprofloxacin ng with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. rofloxacin should be discontinued at the first appearance of a skin rash or any sign of other hypersensitivity tion.

rystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine laboratory animals (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION). stalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. ents receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The mmended daily dose should not be exceeded.

lteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND MINISTRATION).

s with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and atopoietic function, is advisable during prolonged therapy.

g Interactions: As with other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to ated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in eased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of phylline should be monitored and dosage adjustments made as appropriate.

uinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may to reduced clearance of caffeine and a prolongation of its plasma half-life.

ntacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciproflox- resulting in serum and urine levels lower than desired; concurrent administration of these agents with ofloxacin should be avoided.

oncomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with a quinolone has been orted to increase the risk of CNS stimulation and convulsive seizures.

robenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

s with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsuscepti- organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If erinfection occurs during therapy, appropriate measures should be taken.

rmation for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The ferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take acids containing magnesium or aluminum.

atients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a gle dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

iprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug ore they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

atients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine.

cinogenesis, Mutagenesis, Impairment of Fertility: Eight in vitro mutagenicity tests have been conducted with rofloxacin and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

s, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative ults:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

g-term carcinogenicity studies in rats and mice have been completed. After daily oral dosing for up to 2 years, re is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

gnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 6 es the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to rofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Patients under the age of 18 were not included in the clinical trials of ciprofloxacin because ciprofloxacin as well as other quinolones causes arthropathy in immature animals. Ciprofloxacin should not be used in children or adolescents (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in [illegible].0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%). Those events typical of quinolones are italicized.

The most frequently reported events, drug related or not, were *nausea* (5.2%), *diarrhea* (2.3%), *vomiting* (2.0%), *abdominal pain/discomfort* (1.7%), *headache* (1.2%), *restlessness* (1.1%), and *rash* (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below.

GASTROINTESTINAL: *(See above)*, painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding

CENTRAL NERVOUS SYSTEM: *(See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.*

SKIN/HYPERSENSITIVITY: *(See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands*, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported (SEE PRECAUTIONS).

SPECIAL SENSES: *blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste.*

MUSCULOSKELETAL: *joint or back pain, joint stiffness*, achiness, neck or chest pain, flare-up of gout.

RENAL/UROGENITAL: *interstitial nephritis, nephritis, renal failure*, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Other adverse events reported in the postmarketing phase include anaphylactoid reactions, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hepatic necrosis, postural hypotension, possible exacerbation of myasthenia gravis, confusion, dysphasia, nystagmus, pseudomembranous colitis, dyspepsia, flatulence, and constipation. Also reported were agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria, vaginal candidiasis; and renal calculi (SEE PRECAUTIONS).

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic—Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Cholestatic jaundice has been reported.

Hematologic—Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal—Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Lower respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro® (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE DESCRIPTION).

References: **1.** Data on file, Miles Inc Pharmaceutical Division. **2.** Barry AL, Jones RN, Thornsberry C, et al. Antibacterial activities of ciprofloxacin, norfloxacin, oxolinic acid, cinoxacin, and nalidixic acid. *Antimicrob Agents Chemother.* 1984;25:633-637. **3.** Guimaraes MA, Noone P. The comparative *in-vitro* activity of norfloxacin, ciprofloxacin, enoxacin and nalidixic acid against 423 strains of gram-negative rods and staphylococci isolated from infected hospitalised patients. *J Antimicrob Chemother.* 1986;17:63-67. **4.** Van Caekenberghe DL, Pattyn SR. In vitro activity of ciprofloxacin compared with those of other new fluorinated piperazinyl-substituted quinolone derivatives. *Antimicrob Agents Chemother.* 1984;25:518-521.

For further information, contact the Miles Information Service:
1-800-642-4776. In VA, call collect: 703-391-7888.

COMMITTED TO THERAPEUTIC EFFICIENCY

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Pharmaceutical Division
400 Morgan Lane
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Commentary

Laparoscopic Cholecystectomy

Threat or Opportunity?

Laparoscopic cholecystectomy is another French revolution. To the best of my knowledge, the procedure was first accomplished in June 1987 by a French general surgeon named Mouret in private practice in Lyons. He already had a wide experience in gynecologic laparoscopic procedures but did not report this landmark operation. Word of the new procedure, however, reached other French surgeons, and in 1988 Prof Francois Dubois of Paris and Prof Jacques Perissat of Bordeaux each performed their first of many hundred procedures to date.

Reports of early experiences with this procedure in France have spread over the continent and across the seas. The procedure is now being performed in several community and university hospitals in the United States and has aroused great interest among the medical and lay communities, along with alarm and concern among some surgeons. There are a number of precedents (such as arthroscopic knee surgery, laparoscopic tubal ligation, and percutaneous renal lithotripsy) in recent surgical history that should provide a framework for working through the process of accepting this new procedure into the armamentarium of general surgery.

Concerns have been raised in relation to the new procedure in several areas. For example, it is difficult to perform a thorough examination of the periampullary area and retroperitoneum by the laparoscopic method. Also, it is more difficult to do routine cystic duct cholangiography and, thus, there is a possibility of overlooking unsuspected bile duct disease. There is also concern about the extension of indications for the procedure to the large number of asymptomatic patients. In addition to these concerns related to patient safety, many surgeons have fears of being "shut out," ie, not being able to be trained or being trained so late that their competitors have a superior edge. In addition, some surgeons find the technique too difficult or too time-consuming for their practice.

While these concerns are worthy of careful examination, the positive aspects of the procedure should be recognized. When successfully accomplished in the indicated patient, the result is satisfying. Generally, the hospitalization is about 1 day and insurance companies welcome the lower costs associated with the short stay. Opinion seems to be firming up among insurers that the surgeon's fee and that of the trained assistant should be at, or only slightly above, the fees for standard cholecystectomy. The patients are happy with the functional and cosmetic results and employers are grateful that sick leaves are markedly reduced with the new procedure. Finally, the procedure accomplishes the ultimate goal in treatment of gallstones: that is, the complete removal of the gallbladder and stones. In this way it is superior to the nonsurgical methods of treatment, which have a lower efficacy and a high recurrence rate.

It is clear that, at the outset, patient selection is of paramount importance. While surgeons experienced in the technique may liberalize their indications, it will be difficult to fully evaluate this procedure without some kind of formal analysis of many cases, as could be done by a registry. The true place for this procedure has yet to be determined fully. It has a steep learning curve and reports of major complications and even fatalities are filtering in. The entrepreneurial exploitation of the procedure in some areas has further complicated the objective analysis of the procedure. An international surgical organization might well be a suitable agency for the collection of such data inasmuch as large experiences with the procedure exist in many countries besides the United States.

The American College of Surgeons has issued a statement that clearly delineates the experience and qualifications of surgeons who do the procedure.

> For optimal quality patient care, laparoscopic cholecystectomy should be performed by surgeons who are qualified to perform open cholecystectomy. Only such surgeons possess the skills to perform biliary tract surgical procedures; such surgeons are able to determine the best method of cholecystectomy; and only such surgeons can treat complications consequent to laparoscopic cholecystectomy.

The Society for Surgery of the Alimentary Tract has approved the following statement that addresses the training and credentialing aspects of this operation.

> The Society for Surgery of the Alimentary Tract recommends that privileges to perform laparoscopic cholecystectomy should be granted by hospital credentials committees only to individuals who meet certain criteria. Individuals who do laparoscopic cholecystectomy should (1) be trained general surgeons with current competence in performance of open cholecystectomy and in the management of the predictable complications of the operation; (2) have expertise in laparoscopy acquired through previous clinical experience or through instruction; (3) have completed an experience in supervised performance of laparoscopic cholecystectomy which included instruction and practice on animals; (4) provide notification to their patients of the surgeon's experience with, and the status of the procedure.

Laparoscopic cholecystectomy is here to stay. Its proper place in the general surgeon's treatment of patients with biliary tract disease will require further experience and analysis of results that must be honestly reported. It is clear that the procedure must be performed and further developed by general surgeons. In particular, the relative efficacy and safety of the electrocautery vs the laser in dissecting the gallbladder must be carefully evaluated. The statements of the American College of Surgeons and the Society for Surgery of the Alimentary Tract will serve as valuable guidelines in the orderly evolution of this revolutionary technique.

Ronald K. Tompkins, MD
Los Angeles, Calif

Special Article

Accreditation

Procedures and Staff Support for the Surgery Residency Review Committee

John T. Boberg, PhD

• The purpose of this article is to give an overview of the accreditation procedures of the Residency Review Committee for Surgery and provide insight into the nature and functions of staff support for the committee. In the process, a better understanding of how the Residency Review Committee itself carries out its tasks should also emerge. What is described here is specific to the Residency Review Committee for Surgery and should not be generalized to other residency review committees.

(*Arch Surg.* 1990;125:1246-1251)

Most readers are, in a general way, aware of what the staff does in gathering the program information forms, preparing them for meetings, and communicating the decisions of the Residency Review Committee (RRC) to programs. This article will fill in some of the details of this process and, at the same time, seek to provide a broader perspective from which to view the procedures of the RRC and the staff's work.

The staff of the RRC for Surgery includes an executive secretary, a committee coordinator, and a senior secretary. In addition, the RRC for Surgery has the support services of a research associate who manages the surgical operative log project and other research activities as requested by the RRC.

A HISTORICAL PERSPECTIVE

Prior to 1950, the American Medical Association and the American College of Surgeons had separate processes for approving hospitals to train surgeons. That year, after multiple preliminary organizational meetings, the two groups, along with the American Board of Surgery, formed the Conference Committee on Graduate Training in Surgery as the first joint effort toward the accreditation of surgical training programs. At that time, by written agreement, the secretary of the committee had a medical degree and was appointed by the American Medical Association. By the same agreement, on a rotating basis, the chairman and vice-chairman of the committee were always from among the representatives appointed by the American College of Surgeons or the American Board of Surgery.

In the course of the tremendous changes in graduate training since 1950, the graduate medical education system became larger and more complex; it eventually was restructured into the Accreditation Council for Graduate Medical Education (ACGME). As part of that evolution, the conference committee became known as the RRC for Surgery; the secretary's position became more functional and was filled by someone not with a medical degree but a PhD. The RRC secretary's role changed primarily to serve the educational process. A somewhat similar development took place among the RRC members. Although appointed by one of three sponsoring organizations (American Board of Surgery, American College of Surgeons, and American Medical Association), they function as education professionals whose goal is ensuring the quality of surgical residency training programs. Two of the last three chairmen have been representatives appointed by the American Medical Association.

The executive secretary, as presently described in ACGME literature, is "a full-time professional with solid credentials in education and expertise in accreditation." The role of the secretary includes the following three functions that may perhaps be characterized as three different hats.

Staff to the RRC

The principal hat worn by the executive secretary is that of RRC staff person. This includes assisting its work by providing all the materials and information preparatory to meetings and communicating and/or carrying out the decisions made at the meeting. The RRC meets three times each year; the 12 members are all volunteers who have other full-time positions. The office of the secretary, therefore, provides a constant focus and steady support for all the business that comes up from day to day and from meeting to meeting in administering the activities of the Residency Review Committee.

Liaison Between the RRC and Its Constituencies

The second hat of the executive secretary is that of communicator to the RRC's constituencies, serving as a conduit of RRC information and of actions and activities. This includes informing program directors and the RRC's sponsoring organizations of the decisions of the committee and being available to respond to questions.

Liaison Between the RRC and the ACGME

The third hat of the executive secretary is that of liaison between the RRC and the ACGME. This includes acting as a clearinghouse of information about ACGME accreditation policies and procedures that affect the work of the RRC and assisting the committee in providing appropriate information about its activities to the ACGME.

THE TRAIL OF A PROGRAM FILE

As indicated above, the office of the executive secretary is more than the executive secretary. More often than not, it is the committee coordinator who handles the day-to-day activities and responds to requests. Among the coordinator's principal responsibilities are the preparation and distribution of the program files to the RRC members for their review, the organization of the materials for use at the meeting, the postmeeting processing of the program files with the actions of the RRC, and the management of all meeting arrangements.

Following the trail of a program file is perhaps the best way to get an overview of the procedures of the RRC and of the primary work of the RRC office and the committee coordinator. A program file begins as a blank set of Program Informa-

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Accepted for publication August 7, 1990.

From the Residency Review Committee for Surgery, American Medical Association, Chicago, Ill.

Reprint requests to Residency Review Committee for Surgery, American Medical Association, 515 N State St, Chicago, IL 60610 (Dr Boberg).

tion Forms. The forms give program directors an organized format for providing a description of their programs to the RRC. Based on the latest revisions of the special requirements for residency programs, the forms cover such topics as the program's organization and facilities; institutional, clinical, and operative statistics; information on current residents and recent graduates; the faculty and their scholarly involvement; the curriculum, with details on rotations, didactic instruction, and clinical conferences; and the operative experience of the recent graduates.

The information provided in the forms becomes the basis for an on-site visit and report by a site visitor who is either a full-time field staff person or a specialist site visitor (see below). The site visitor's report is returned to the office of the RRC along with the forms. The committee coordinator then organizes the forms into a *program file* that comprises (1) the history sheets summarizing the previous recommendations and actions of the RRC and the ACGME concerning the program, (2) the program information forms, (3) the site visitor's report, and (4) any relevant correspondence that has been received since the last RRC review of the program or since the site visit (eg, updated or corrected information that resulted from the site visit). To this documentation the coordinator adds a face sheet that highlights the request(s) included in the file; for example, the addition or deletion of a participating institution or a permanent or temporary increase in resident complement. In organizing the file, the coordinator reviews the forms to determine whether the relevant program information has been included; if some information is missing, the coordinator may request it from the program director.

Once the file is organized, the coordinator prepares it for distribution to the RRC members for review. The policy of the RRC for Surgery is to have two reviewers for programs that are liable to the withholding or withdrawing of accreditation (new applications or programs with provisional or probationary accreditation), as well as all programs that have requested reconsideration after an adverse accreditation action. In the latter case (programs under reconsideration), the two reviewers are always different from those who reviewed the program at the previous meeting. Single reviewers are used for other programs, including those that are presenting interim requests that do not include an accreditation status, such as a request to increase the resident complement.

During the past few years, while the RRC for Surgery was in transition relative to use of the surgical operative log as part of program review, copies of these logs were also added to the program file in addition to the resident records. With the revised forms, the surgical operative log reports are already part of the program information forms so that the file is not so large.

When the RRC members complete the review of the programs they have been sent, they return each file to the coordinator. To allow sufficient time for the RRC members to review the program files adequately, the coordinator closes the agenda for a meeting about 8 weeks before the scheduled date. This closure is occasionally a cause for consternation to program directors who expected or desired to have their programs reviewed at a particular meeting of the RRC. One of the factors that affects getting programs on a particular agenda is the length of time required by site visitors to get their reports to the office of the RRC. It usually takes 4 weeks for reports to arrive at the RRC office after the site visit, but any number of circumstances may extend that period. On the other hand, program directors are often not cognizant of the dates of RRC meetings and are chagrined to learn that their last-minute request cannot be considered until 4 to 6 months later.

THE MEETING ITSELF

Since 1986, the RRC has met three times each year, usually in February, June, and October. The average number of programs considered at a meeting is 70. The programs are considered individually, with each reviewer presenting his or her analysis and recommendation. The RRC then discusses the analyses and may question the primary reviewer(s) about the documentation contained in the program file or about the reasons for the recommendation. Usually consensus on the program is reached by the whole committee; on rare occasions, when consensus cannot be reached in a reasonable amount of time, a vote is taken by a show of hands.

During the review of programs, the RRC members are guided by the ACGME policies on conflict of interest. If a conflict is identified, the members are to withdraw from all deliberations of the issue under discussion and leave the meeting room. Minutes of the meeting are to reflect this action.

The amount of time spent discussing any individual program depends on the nature of the decision required by the RRC: Is the decision an accreditation action, a reconsideration, a progress report, or a request for an additional participating institution or for additional residents?

The meeting time spent on programs is, of course, in addition to the amount of time the RRC members have spent on their review of the programs. For purposes of gross calculation of contributed services by physicians in all specialties to the accreditation process, John Gienapp, PhD, executive secretary of the ACGME, has estimated 1 hour as the average time for review. For recent years at least, 1 hour is a very conservative estimate for the RRC for Surgery.

A RECORD OF ACTIONS

The Table gives a summary of the number of programs reviewed and the type of decisions reached at the RRC meetings of the last 15 years. A total of 2669 programs were reviewed, about 178 annually; 1843 decisions concerned the accreditation status of programs. Of the 1843 status decisions, 70.4% were positive accreditation decisions, 21.2% were adverse decisions, and 8.4% were deferrals.

The increased number of provisional actions noticeable in 1977-1978 reflects the transition from 4-year to 5-year programs and the introduction of the accreditation of pediatric surgery programs; a smaller increase in 1984-1985 reflects the start of the accreditation of vascular surgery programs. Figure 1 shows an overview of all the decisions made by the committee: 48.6% of the 2669 reviews were positive accreditation decisions, 14.6% were adverse accreditation decisions, 8.8% were reconsideration decisions, and 27.9% were miscellaneous decisions which include deferrals, decisions about nonaccreditation issues (resident complement, addition of affiliated institutions, etc), and reviews of progress reports.

Figure 2 shows the breakdown of the program reviews year by year. The small number of programs reviewed in 1977 reflects the fact that due to rescheduling, only one meeting was held that year. The relative number of adverse actions indicates some variability over the years, with a small decline in the most recent years. This variability is further highlighted in Fig 3, which shows the number of adverse and positive accreditation actions each year.

POSTMEETING ACTIVITY

The main postmeeting activity is the production of the letters of notification. Based on the discussion and the decisions on each program reached at the meeting, the executive secretary writes a statement that expresses the decision of the RRC. This text along with other information pertinent to

Activity of the Residency Review Committee for Surgery*

Year	No. of Programs on Agenda	Total Status Decisions	Positive Actions		Adverse Actions					Total Reconsiderations
			FA/CF	PV/CV	Total	% of Total Status	PR/CR	WD	WH	
1975	196	166	81	23	49	30	30	16	3	12
1976	153	134	57	28	28	21	21	5	2	2
1977	64	56	23	14	13	23	4	8	1	1
1978	223	177	57	64	42	24	17	16	9	11
1979	132	97	45	29	14	14	5	6	3	16
1980	135	106	58	21	20	19	11	7	2	4
1981	156	122	66	22	28	23	19	8	1	11
1982	205	137	73	17	37	27	20	15	2	31
1983	170	91	50	7	19	21	9	5	5	26
1984	230	144	48	23	42	29	5	9	28	24
1985	233	142	63	20	33	23	12	13	8	29
1986	170	98	63	14	16	16	7	2	7	24
1987	201	111	69	7	15	14	7	4	4	21
1988	191	120	50	21	18	15	7	7	4	15
1989	210	142	68	14	17	12	8	3	6	8
Total	**2669**	**1843**	**871**	**324**	**391**	21	**182**	**124**	**85**	**235**

*FA/CF indicates full/continued full accreditation; PV/CV, provisional/continued provisional accreditation; PR/CR, probation/continued probation; WD, withdrawal; and WH, withhold.

the review of the program makes up the Chairman's Document. For each program reviewed at a meeting, a document is sent to the chairman of the RRC for his or her correction or approval and signature. The chairman's signature verifies that the text expresses the decision of the RRC and authorizes the letter to be sent to the program director.

The letter of notification indicates the accreditation status of the program and any specific comments recommended by the RRC. It includes the actual text as approved by the chairman, other information pertinent to the accreditation process, and the approximate time of the next site visit. The time to the next survey may range from 1 to 5 years; the average is 3 years. In the letter, program directors may also be requested to submit progress reports to clarify information provided earlier or verify that some change has actually occurred as indicated in the earlier submission.

Another statement sometimes included in the letter of notification is that the next survey will be carried out by a specialist site visitor. If no mention of the type of survey is made, the site visit will normally be conducted by one of the full-time field staff members. In recent years, the use of specialist site visitors by the RRC for Surgery has significantly decreased. An analysis of the type of "previous" and "next" site visits for programs reviewed by the RRC from October 1987 through February 1990 indicates that 100 (32%) of the programs reviewed for accreditation action during these meetings had had a specialist site visitor, whereas only 25 (8%) of them were projected to have one for the next site visit.

There are occasions, however, for which the RRC believes that a surgeon is the best person to gather information about a program and/or clarify certain conditions. The committee, therefore, is concerned to maintain a cadre of specialists on whom it can depend when needed.

The amount of time required to produce the letters of notification varies considerably from specialty to specialty; it is related primarily to the number and type of programs reviewed at a meeting, but other scheduled activities and travel are factors also. For the surgery RRC, as indicated above, the number of programs at recent meetings has averaged about 70, and it is usually 2 months before all the letters are sent out. This period includes writing up the text of the decision, getting the official documents signed by the chairman, and mailing out the letters. Letters are generally first sent to those directors whose programs may be returned to the next RRC meeting; that is, those programs that were deferred for more information and those that received an adverse accreditation action.

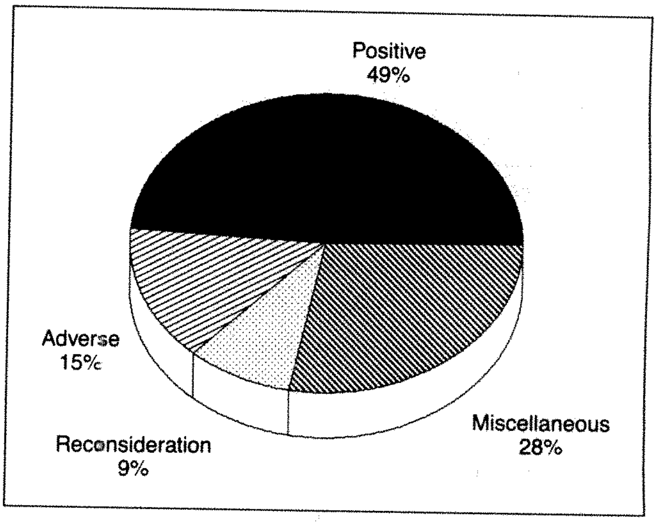

Fig 1.—Fifteen-year overview of agenda items. Combined figures represent general surgery, pediatric surgery, vascular surgery, and surgical critical care.

EMPHASIS ON COMMUNICATION

Another very important factor in the length of time required to send out letters is an increased emphasis on communicating to program directors the basis of the decision reached by the RRC, particularly when dealing with an adverse action. Checking the decisions and presenting them in a concise but adequate manner can be tedious and time-consuming. The goal is to maintain consistency and objectivity in the RRC's

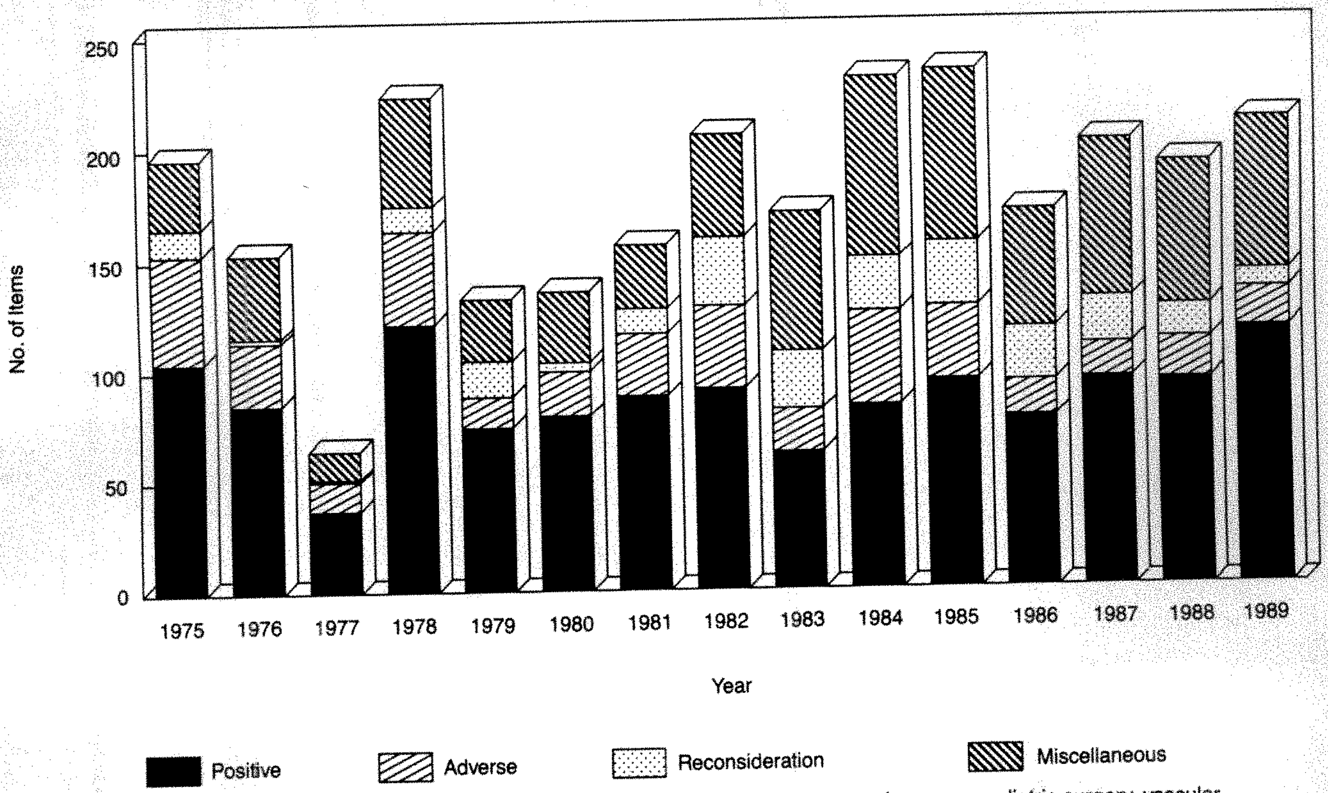

Fig 2.—Breakdown of agenda items each year. Combined figures represent general surgery, pediatric surgery, vascular surgery, and surgical critical care.

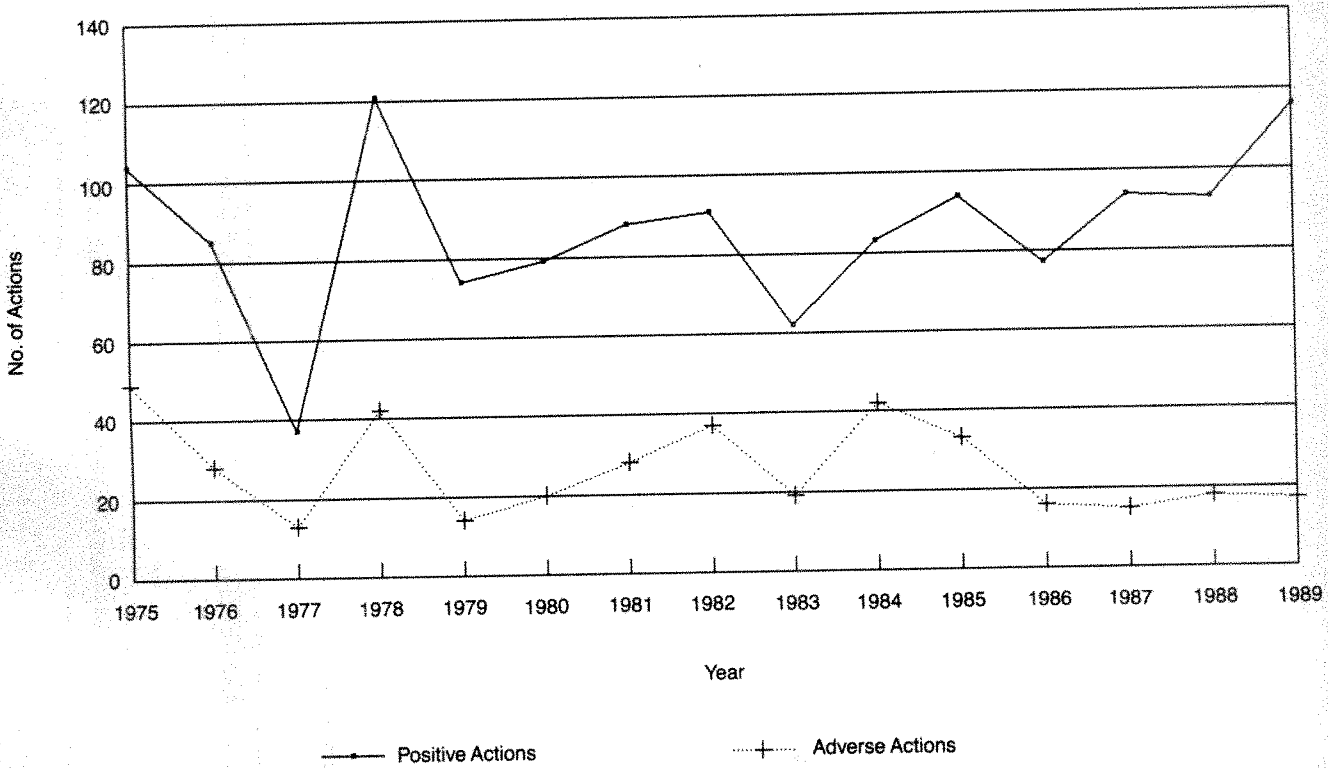

Fig 3.—Positive vs adverse actions. Combined figures represent general surgery, pediatric surgery, vascular surgery, and surgical critical care.

communications, particularly with regard to operative experience.

The surgical operative log, of course, has been a key factor in helping the RRC achieve consistency in its evaluation of operative experience. This project, which is now in its fifth year, has provided an annual database to guide the RRC in its evaluation of programs and in establishing specific guidelines for operative experience. Sending program directors the surgical operative log reports of the program as well as of their individual residents has been an important piece of shared information.

The introduction of a newsletter has also been a major step toward greater communication. The goal has been to keep the RRC's constituencies apprised of its thinking and decisions, especially concerning the way the committee understands and applies certain standards of the general and special requirements. At the same time, another very important type of communication has been going on inside the RRC itself. In each of the last 4 years, the committee has taken an extra "retreat" day at one of its regular meetings to discuss policy issues and long-range goals and objectives. Some policy discussion takes place at each RRC meeting, but with the large number of programs normally on the agenda it is difficult to handle larger and more complex issues. The following topics were covered at the February 1990 meeting: educational issues and revision of special requirements for vascular surgery and for surgical critical care, issues and directions dealing with specialization/fragmentation of the specialty of surgery, revised guidelines for operative experience and simpler reporting of same, and revision of the special requirements for education in the subspecialties of surgery.

MONITORING THE RRC

As indicated above, the RRC for Surgery is part of the overall accreditation organization of the ACGME. Just as the formation of the Conference Committee on Graduate Training in Surgery in 1950 was the result of efforts to standardize and unify the approval of surgery training programs, broader efforts were made in the 1970s to bring greater coherence and efficiency to the growing number of specialties and programs involved in graduate medical education. As a result of these efforts, the ACGME is the nationally recognized accreditation body that delegates authority to the RRCs to carry out the accreditation activities for programs in the pertinent specialties and subspecialties.

The ACGME exercises its oversight of the individual RRCs through several mechanisms, including the approval of standards for training, a standing committee that periodically monitors the practices and accreditation actions of the RRCs, and an appeals process that maintains the ACGME as the final decision maker for any particular accreditation decision.

The monitoring committee presently reviews the individual RRCs approximately every 3 years. This ACGME committee looks at the minutes of RRC meetings for the most recent year, including the list of all the accreditation actions taken at a meeting, and evaluates them in the light of the policies and procedures of the ACGME. On the basis of this review, the committee recommends—or does not recommend—continued delegated authority to the respective RRC and sets the time of the next oversight review.

The appeals process, which was first approved in 1976, is a mechanism that allows program directors to challenge adverse accreditation actions to a level beyond the RRC and to receive a hearing before a specially established panel of three specialists in the pertinent field. The purpose of the panel is to review the written record and receive the written and oral presentations of the program to make a recommendation to the ACGME on whether there was substantial, credible, and relevant evidence to support the action taken by the RRC; in addition, the panel will make recommendations as to whether there was substantial compliance with the administrative procedures governing the process of accreditation of graduate medical education programs. The ACGME then acts on the appeal at its next regularly scheduled meeting.

Since 1979 when the first appeal was held, the RRC for Surgery has had the largest number of decisions appealed. Of the 44 accreditation decisions (probation, withhold, or withdraw) that were appealed, 27 (61%) were upheld and 17 (39%) were reversed through the appeals process. Of the decisions to withdraw, 21 (70%) were upheld and 9 (30%) reversed. In addition, three resident complement decisions were appealed; all were reversed.

FUTURE DIRECTIONS

The purpose of the RRC for Surgery will remain the establishment and oversight of educational standards for the accreditation of surgical residency programs to ensure quality education and excellent patient care. Progress in medical science and technology will continue to be a challenge both to the specialty and to the RRC to respond positively and creatively to the ever-changing environment of health care. The record of the past 40 years is a good indicator that the committee will meet the challenge.

Patricia Surdyk and Karen Pleasant of the ACGME research department assisted in the statistical reports and graphs.

Forty Years of the RRC in Surgery

The RRC (Surgery), the American Board of Surgery, and the American College of Surgeons are the quality control mechanisms of American graduate surgical education. The RRC is now completing its 40th year of intense deliberations. In this article, Dr Boberg, Executive Secretary of the Committee, has detailed the activities of the RRC in accrediting surgical graduate training programs in the United States.

The RRC for Surgery is one of 24 established RRCs. One exists for each of the medical specialties; eight involve surgical disciplines. Certification is provided by their respective specialty boards. The RRC for Surgery is concerned with the assessment of training programs, in contrast to the American Board of Surgery, whose activities relate to the certification of individuals. Of the 6570 accredited programs involving 89 000 residents, 2110 (32%) received regular accreditation status review in 1989. Each RRC develops special requirements for its own training programs.

The ACGME is sponsored by the American Board of Medical Specialties, American Hospital Association, Association of American Medical Colleges, the Council of Medical Specialty Societies, and the American Medical Association. On recommendation by the RRC and approval by the ACGME, guidelines for these programs contain the essential educational content, instructional activities, patient-care responsibilities, supervision, and facility requirements.

The general requirements outline program guidelines and responsibilities common to all RRC institutions regardless of the specialty. These requirements are also established by the ACGME in collaboration with the respective RRC and its sponsoring organizations. An assessment of whether the institutions fulfill the general requirements is made in the review process of their graduate programs. Accreditation of a residency program indicates that it is judged to be in substantial compliance with the essentials of accredited residencies.

The RRC of Surgery consists of 12 active members, four nominated by each of the sponsoring organizations: the Council on Medical Education, American College of Surgeons, and American Board of Surgery. Three ex-officio nonvoting members are added: the Executive Director of the American Board of Surgery, the Associate Director of the American College of Surgeons, and the Secretary of the RRC for Surgery. The duration of the appointment of active members is 6 years. The chairman is elected by the committee and usually serves for 2 years. The RRC reviews program information in detail, determines the degree to which it meets the published guidelines, decides on an accreditation status for the program, and identifies areas of noncompliance with the standards.

During these 40 productive years, 18 chairmen and 78 members have served on this committee voluntarily. The following lists include the names of the chairmen and members:

Residency Review Committee Chairmen

Frederick A. Coller	1950-1956
Lawrence Chaffin	1956-1957
Warren H. Cole	1957-1959
John H. Mulholland	1959-1961
John H. Gibbon, Jr	1961-1963
William P. Longmire, Jr	1963-1965
William D. Holden	1965-1967
Howard H. Bradshaw	1967-1969
Robert J. Coffey	1969-1971
Samuel P. Harbison	1971-1973
Harry W. Southwick	1973-1977
W. Dean Warren	1973-1979
John L. Sawyers	1979-1981
John J. Byrne	1981-1983
Hiram C. Polk, Jr	1983-1985
J. Roland Folse	1985-1987
William Silen	1987-1989
Paul Friedmann	1989-present

Residency Review Committee Members

Alfred S. Blalock	1950-1953
Guy A. Caldwell	1950-1953
Peter Heinbecker	1950-1953
Harvey B. Stone	1950-1953
Calvin M. Smyth	1950-1955
Lawrence Chaffin	1950-1957
Frederick A. Coller	1950-1957
Warfield M. Firor	1950-1958
Warren H. Cole	1950-1959
John D. Stewart	1950-1959
Leland S. McKittrick	1954-1957
Robert M. Zollinger	1954-1961
John H. Mulholland	1955-1961
John M. Waugh	1957-1962
Gustaf E. Lindskog	1957-1963
Robert M. Moore	1957-1963
Walter G. Maddock	1958-1962
Charles W. McLaughlin, Jr	1958-1963
John H. Gibbon, Jr	1959-1965
William P. Longmire, Jr	1959-1966
J. Englebert Dunphy	1961-1967
William D. Holden	1961-1967
James D. Rives	1962-1965
Jonathan E. Rhoads	1963
George H. Yeager	1963-1968
Howard H. Bradshaw	1963-1969
Carl E. Lischer	1963-1969
Claude E. Welch	1963-1969
Harold A. Zintel	1965-1969
Robert J. Coffey	1965-1971
William H. Muller, Jr	1966-1972
Samuel P. Harbison	1967-1973
K. Alvin Merendino	1967-1973
Harwell Wilson	1969-1974
Donald Mulder	1969-1975
William H. Moretz	1969-1975
Merle M. Musselman	1969-1975
Fiorindo A. Simeone	1970-1975
Harry W. Southwick	1971-1977
John M. Beal	1972-1978
F. William Blaisdell	1973-1979
W. Dean Warren	1973-1979
H. William Clatworthy, Jr	1974-1980
George L. Jordan, Jr	1974-1980
Donald McIlrath	1974-1980
Peter Dineen	1975-1980
Robert E. Hermann	1975-1981
Victor Richards	1975-1981
John L. Sawyers	1975-1981
George L. Nardi	1976-1978
John J. Byrne	1978-1983
Hiram C. Polk, Jr	1978-1985
James W. Pate	1979-1984
George F. Sheldon	1979-1985
Robert Zeppa	1979-1985
E. Thomas Boles, Jr	1980-1986
Robert E. Condon	1980-1986
Jeremiah G. Turcotte	1981-1986
Arthur J. Donovan	1981-1987
J. Roland Folse	1981-1987
G. Robert Mason	1981-1987
Robert M. Zollinger, Jr	1982-1987
William Silen	1983-1989
H. Harlan Stone	1985-1988
Roger T. Sherman	1985-1990
J. Bradley Aust	1985-present
Paul Friedmann	1985-present
R. Peter Altman	1986-present
Claude H. Organ, Jr	1986-present
Jay K. Harness	1987-present
Olga M. Jonasson	1987-present
Samuel A. Wells, Jr	1987-present
W. Gerald Austen	1988-present
Lester F. Williams, Jr	1988-present
Robert Barnes	1988-present
Frank Lewis	1989-present

The RRC has been directed by respected leadership in its chairmen and committee members. Forty percent of the chairmen and RRC members have been presidents of regional surgical societies. A significant number of the RRC chairmen have been presidents of the American Surgical Association. Fifty-six percent of the chairmen and 40% of the committee members graduated from medical school at either Harvard University (Cambridge, Mass) or Johns Hopkins University (Baltimore, Md). Twenty percent of the RRC chairmen completed their residencies at Washington University (St Louis, Mo). The following is a list of RRC executive secretaries who have played vital management and communication roles in committee activities.

RRC Executive Secretaries

E. H. Leveroos, MD (deceased)	1953-1956
Willard V. Thompson, MD	1956-1972
Paul A. Van Pernis, MD	1972-1977
Adelwin Douherty, PhD	1978
Mary Alice Parsons	1979-1981
Judith S. Armbruster, PhD	1981-1986
John T. Boberg, PhD	1986-present

The current associate staff members, Patricia Surdyk and Marsha Stojek, are vital in coordinating a vast amount of review material for the committee, collating data, developing the annual RRC database, and keeping in contact with the committee.

The RRC has 280 general surgery programs under assessment and reviews the experiences of 990 to 1000 chief residents each year. In addition, there are 49 ACGME-approved vascular fellowships involving 80 vascular fellows, and more recently, five approved critical care fellowships in surgery with nine residents. Currently there are no RRC-approved hand fellowships. Review of the special requirements for their relevance and practical application is ongoing. Committee decisions are detailed, well documented, and fair. There are appropriate mechanisms for appeal of adverse decisions of the committee as part of its due process.

There is an excellent level of cooperation between the RRC, the American Board of Surgery, and the Association of Program Directors in Surgery. This close interaction has led to an improved understanding of their mutual problems. Although the nature of RRC actions does not breed uniform popularity, respect for its decisions has increased in recent years. Committee members commit significant time each year to RRC activities. The acceptance of membership on this committee requires attendance of three meetings each year that last for 2 to 3 days and demands considerable time for committee work at home. It becomes readily evident that this committee and its activities constitute a major commitment by American surgeons to maintain high-quality training programs. Volunteer surgeons conduct site visits for general surgery training programs and specialty fellowships. Mindful of the steady course the RRC has maintained over 40 superb years of graduate surgical education, the ARCHIVES salutes the RRC, current and past chairmen, and committee members for a job well done.

CLAUDE H. ORGAN, JR, MD
Oakland, Calif

Papers Read Before the 61st Annual Meeting of the Pacific Coast Surgical Association, Laguna Niguel, Calif, February 18 to February 21, 1990

Humanism and the Profession of Surgery in the Era of Medical Perestroika

Eric W. Fonkalsrud, MD

The physician needs a clear head and a kind heart.
SIR WILLIAM OSLER

It is impossible to adequately express to the members of the Association my gratitude for the privilege of serving as your president. To be so recognized by my friends and colleagues instills deep feelings of humility and of pride for this singularly great honor, and I shall be forever grateful for your confidence and support. I am keenly aware that the combination of your generosity and my good fortune does not endow me with any profound wisdom or magic solution to the many difficult problems currently confronting the field of surgery in the United States. I also realize that it is rare that one has the opportunity and privilege of discussing a personally selected subject before a semi-captive audience with the sophistication of the Pacific Coast Surgical Association. As physicians, and particularly as surgeons, we have been recognized as professionals. Since King James IV of Scotland in 1505 granted the Charter of Privileges, which established the Royal College of Surgeons of Edinburgh, surgeons have been identified as having skills and responsibilities greater than those of the barbers and laborers of the time. During the ensuing years, surgeons and physicians have been held in high esteem and trust largely because of the unique skilled care that they have provided on a personal basis to their patients; they were thus accorded the privilege of being considered professionals. Since we are currently in the midst of extensive social change that is associated with rapidly expanding technology and broad alterations in our system of health care delivery, I would like to address my few comments to humanism, one of the most important elements of the profession of surgery in this era of medical restructuring and reassessment, or, as Mikhail Gorbachev has called it, "perestroika."[1]

THE AGE OF MEDICAL TECHNOLOGY

We have entered an era of enormous and rapid advancement in technology, particularly in the field of medicine. Our science is speeding into the future. The media and the public are excited about the frequent reports of new diagnostic and therapeutic modalities, and even basic concepts such as genetic engineering. We, as the developers and users of these new technological advances, are even more excited, and are spurred on to achieve new medical breakthroughs with increasing vigor and intensity. Perhaps no area in medicine has experienced a greater explosion of new developments than the field of surgery. Within the past two decades, coronary artery revascularization, organ transplantation, joint replacement, extracorporeal membrane oxygenation, lithotripsy, fiberoptic endoscopy, laser coagulation, and many other surgical techniques have not only been developed, but have become some of the most frequently used procedures in our surgical armamentarium.

Eric W. Fonkalsrud, MD

The acceleration of technology, and new concepts and commitments to health care provision, termed "medical future shock," have made it difficult for the conscientious physician to establish a clear set of priorities for his or her time.[2] Since the end of World War II, as the science of medicine has rapidly evolved, the craft has gradually overtaken the art. Because our mission is to promote both the *science* and the *art* of surgery, we should strive for a balance of the two. As Dr Alan Nelson[3] notes in his presidential address to the American Medical Association in 1989, "We must pause and reflect on the role of humanism in medicine, on that part of our professional calling that denotes the responsibility we have for caring, and the relationship between our art and our science."

In our academic medical centers, there has been an increasing tendency by many physicians to seek achievement in research rather than in teaching and in clinical care. Dr Robert Petersdorf,[4] president of the Association of American Colleges, notes that our present system provides incentives and rewards for more gadgets and "high tech" research, but provides minimal rewards for humanism; teaching and sometimes patient care take a back seat to research. Sheehan and associates[5] recently reported that in a pilot study of third-year medical students, over three fourths have become cynical about academic life and the medical profession as a result of mistreatment by faculty and house staff. In the absence of enthusiasm, dedication, and caring on the part of their teachers, it was suggested that students are likely to become less effective physicians.[6] In his last public address Dr Alfred Blalock,[7] who was one of the first surgeons in this country to develop an active surgical physiology laboratory, stated that "the paramount consideration is the rendering of the best possible care to the human being with a real or fancied illness. . . ." He further indicated that excellent patient care, teaching, and clinical research should be accorded a status of dignity equal to that of so-called basic laboratory research.

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From the Department of Surgery, UCLA School of Medicine, Los Angeles, Calif.

Presented as the presidential address at the 61st Annual Meeting of the Pacific Coast Surgical Association, Laguna Niguel, Calif, February 19, 1990.

Reprint requests to the Department of Surgery, UCLA School of Medicine, Los Angeles, CA 90024 (Dr Fonkalsrud).

MEDICINE: A PROFESSION OR A BUSINESS?

Coupled with the rapid advancement in medical technology, concern has been expressed regarding the insidious progression of medical care from a profession into a business.[8] As noted by Dr Richard Ahlquist[9] from this Society, the high quality of medical care, possible as a result of the heavily supported programs of biomedical research, has become increasingly inaccessible because of the almost logarithmic increase in cost. When Medicare and Medicaid were signed into law in 1965, the government viewed access to health care as a right of all citizens. As noted by Paul Starr,[10] this legislation also changed that portion of physicians' and hospitals' work that was once philanthropic to work seeking at least some reimbursement. O'Neill[11] observed that this legislation was a major stimulus to the monitorization of medical care, and a great impetus to the rise in the cost of health care in the United States. Hospitals have been encouraged to buy newly developed technology and to organize as for-profit enterprises. Encouraged by the Health Maintenance Organization Act of 1974, large investor-owned corporations structured their health provision organizations to not only control cost, but to provide a profit. This initiated a trend that has progressively undermined the physician-patient relationship. The patient-subscriber has become a contractor with a system, not a physician, a factor that has tended to diminish the personal commitment of the physician to his or her patients, potentially undermining quality, and the close relationship that has for generations been the most gratifying aspect of a physician's life.

Since we physicians consider ourselves to be professionals, further definition of this term and its major characteristics are in order. A "professional" possesses expertise, formal education, and special competence—an entitlement to act independently, a measure of autonomy.[12] A professional does what he or she does for reasons besides money. He or she hews to high ethical standards, consciously conforms to a code, feels a sense of service to humanity, and acknowledges a higher responsibility than just earning a living. Ethics is one of the major characteristics that distinguishes a professional from a technician. In addition to the elements of expertise, autonomy, and higher calling the essence of being a professional is *trust*. The patient needs to trust the surgeon because the patient cannot perform surgery and must, therefore, rely on the surgeon. *Altruism*, an unselfish concern for or devotion to the welfare of others, is a hallmark of the medical professional. Surgeons must possess great technical skill and scientific knowledge, and must reaffirm their place in our society as professionals in the full sense of the word if they are to retain the trust of their patients, and of our government.

CORPORATE INFLUENCE ON MEDICINE

Although the work of the professional is recognized as entailing altruistic sacrifice as well as craftsmanship, in this society, in which financial rewards for hostile corporate takeovers and leveraged buyouts are great, it is tempting for physicians to become deeply entrepreneurial in their work as the successes among their peers outside medicine are often measured in dollars and not pride. As Dr Julius Krevans,[13] chancellor of the University of California, San Francisco, notes, "Individual physicians, groups of physicians, teaching hospitals, as well as third-party insurers, have all begun to behave more like a trade. In turn, the entities with which we deal, government or commercial, have begun to think of us that way; and when they think of us that way, we behave even more that way."

The pressures of financing and maintaining the necessary patient flow have led physicians into the modern world of advertising, mergers, acquisitions, for-profit subsidiaries, and joint ventures. Our very language in medical practice has changed to include new buzz words, such as marketing, consumers, and providers—a far cry from the personal relationship between physician and patient that Dr John Stevenson,[14] in his presidential address last year, described so well as "the surgeon, healer with work at hand." Medicine is no longer the laying on of hands; it is more like reading the signals from machines. In the past, the surgeon could work as an independent, compassionate, and caring physician, performing the appropriate operation and simply collecting a fee. The fierce complexity of the various reimbursement schemes has driven the solo practitioner into group practice with a business manager trained in marketing and public relations with the ability to cope with Medicare, preferred provider organizations, diagnosis related groups, categories, classes, rules, exceptions, and so on.

New technology in surgery and medicine has heretofore been provided for the benefit of patients and physician colleagues, with the accolades for achievement being both the reward and incentive. The new corporate and for-profit thinking in science has directed increasing attention toward patents and the concept of individual or corporate-owned information; yet it is not clear that the logarithmic increase in medical innovations have all truly been in the public's best interest. It has been noted that the hospital charges, rather than the professional fees, are the principal cause of the rising health care costs.[15] So long as the professional provider is not personally at risk for the cost of the care that he or she orders, it is unlikely that we will arrive at a more rational and economic use of technology. Medicine has entered the world of big business, toward which the US government has, for some years, maintained a staunch antitrust posture. We find that our profession, which depends so strongly on the personal trust between patient and physician, may now be required by law to demonstrate an antitrust position with respect to the provision of health care.

What then is the effect on the individual, the professional, the surgeon of our society's rapid progression into an era of high technology, corporate medical care, and restrictions placed by government? Schwartz (*New York Times*. March 1, 1975:18) has noted that more laws affecting medicine have been passed in the last decade than in all US history. Government is increasing the stringency of its controls on all aspects of medical care, regardless of who pays for it. Every quality care control expert and statistician is familiar with the bell-shaped or gaussian curve and how it describes the way otherwise identical things vary. As Kanigel[12] notes, to move professionals into large corporations is likely to "lop off the tails on either end of the curve—to reduce the number of bad apples among them, but also to inhibit or discourage the best." The work is more likely to be monitored and controlled. This will result in better work, on the average, and cost the patient less, but that is the average. There is a tendency for government and industry to bring standard solutions to nonstandard problems. The overall effect—creativity and genius—may be worn down or even driven out, but so will those at the lower end of the curve who have abused the system. This scenario may be the ultimate consequence when physicians are no longer trusted, when they are squeezed and constrained by the new harsher circumstances of their work, a progression toward mediocrity.

A student who learns medicine in an environment where the goal is cash flow rather than personal dedication, compassion, and the accessibility or the quality of health care will become a different kind of physican than someone educated in an atmosphere in which the goal is the satisfaction of the patients' needs. The 1989 American Medical Association Public Opinion Survey indicated that less than one third of the public believes that physicians explain things well or spend enough time with their patients.[3] Approximately two thirds of Americans think that physicians are too interested in making money and don't care about people as much as they used to. Patients increasingly tend to view physicians more as technicians than as healers. Medical technology is, furthermore, often experienced as invasive and dehumanizing.

HUMANISM: THE ESSENCE OF MEDICINE

According to Eli Ginzberg[16] of Columbia University (New York, NY), "The American public has not yet come close to giving up their private physician for an investor-dominated management corporate approach designed for profit." The driving force of stock profits as the major goal, rather than producing a quality product, has become all too common in corporate ventures. This type of thinking has no place in the field of medicine. The ability to provide the miraculous cures of the future will depend on our understanding and application of the art, as well as the technology, of medicine. The confidence of the public, the bestowing of professional freedom, and the exchange of trust between patient and physician are based on those values that embody the art of medicine, the art of caring, which includes humanism, diligence, altruism, moral character, adherence to ethical standards, judgment, and knowledge.

One of the most important elements of the profession of surgery is *humanism*, which has been defined as a mode of thought or action in which human interest, values, and dignity are taken to be of primary importance.[17] In applying humanistic principles to our relationships with patients, we must be sensitive to their needs, manage our time so their waiting is limited, respect their dignity, understand their desire for information, and respect their right to participate in decisions. One of the most important differences between a professional and a nonprofessional is the pride and honor that one obtains from his or her work and productivity. The pride of seeing another person's life benefit from your endeavors is almost unique to the medical profession.

The surgeon is particularly privileged as a professional, as is noted by Dr Carl Schlicke[18] in his address to the Pacific Coast Surgical Association 12 years ago: "Who better than the surgeon is aware of the awesome responsibility which is his when a trusting patient places his life in his hands, when a split-second decision in the operating room, a move of the hand, can make a difference between life and death. . . . it is not surprising that to many surgeons their calling becomes almost a religion with the operating suite the temple of their devotions."

This concept has been the basis of our medical practice for centuries and is well phrased in the Hippocratic Oath that states, "To the best of my ability and judgment I will practice the art of medicine only for the benefit of my patients." Maimonides has provided the soul for the physician in his well-chosen words, "May the love for my art activate me at all times. May neither avarice nor miserliness, nor the thirst for glory, nor for a great reputation engage my mind; for the enemies of truth and philanthropy could easily deceive me and make me forgetful of my lofty aim of doing good to thy children. . . . Oh God, thou has appointed me to watch over the life and death of thy creatures."

WHERE DO WE GO FROM HERE?

How do we go about increasing the confidence and trust of the public? The problems of health care are both societal and medical, and the solutions are complex. As lack of pride and workmanship pervades many areas of business in our society, we can do much by educating the public and ourselves, and maintain an unswerving pursuit of excellence. The public must understand the expectations we place on ourselves and then we must live up to those expectations.

A rededication of our efforts to a more humanistic approach to patient care will do much to promote a better relationship with our patients. They must have a feeling that we are genuinely interested in them and that we have a firm personal commitment to their welfare. The art of medicine explains the science in such a way that the patient understands his or her disease and treatment, and recognizes that the physician is committed to sharing the future with him or her.

As Francis Peabody[19] in his landmark article in 1927 entitled "The Care of the Patient" wrote, "One of the essential qualities of the clinician is his interest in humanity, for the secret to the care of the patient is in caring for the patient." A patient must be completely confident in the sympathetic understanding of the physician as well as in his or her skill.

Although humanism is to be welcomed as a long-overdue reaction to our preoccupation with scientific and entrepreneurial medicine, idealism alone is not an adequate guarantor of social usefulness. Traditionally, the physician's concern for the patient has been unaffected by quotidian concerns. Society has encouraged physicians to seek the highest levels of ethical and selfless behavior. Concomitantly, physicians have been provided a privileged place in society and are able to afford all of the necessities and even many of the luxuries of life. Such surgical elitism in our egalitarian society can only be justified by the offering of certain sacrifices and the acceptance of certain restrictions, for with privilege comes responsibility. As Weinstein[20] has noted, the staff of Aesculapius, the mythical god of medicine, has but a single serpent. Hippocrates, considered to be the father of medicine, incorporated his reverence for the profession into the oath that is still taken by medical graduates, and that we as physicians use to reaffirm our belief in the primacy of patient interest. In contrast, the caduceus of Hermes has two serpents intertwining around the staff. In Greek mythology, Hermes was the god of commerce as well as science, eloquence, and cunning. Physicians should not be encouraged to emulate the god of mercantilism. As Weinstein notes further, "American society has not served itself well by allowing medical ethics to be equated with business ethics. The second serpent should be excised from the staff of Aesculapius and never allowed to return."

SPECIFICS FOR THE FUTURE

As privileged professionals or, to quote Schwartz,[21] "eagles in an egalitarian society," we must accept certain responsibilities, some of which have been suggested by a few of our surgical colleagues in previous presidential addresses.[22,23] We must demonstrate those qualities of professional behavior and interpersonal relationships that characterize the accepted ethical standards of a responsible physician and an effective member of society. The major qualities of surgical excellence should include *caring, concern for the common good, commitment, competence, creativity, compassion,* and *confidence.*

We must care about the effective provision of our medical and surgical services with a personal concern for the common good of our society. In conjunction with both government and industry, we must develop a modern and cost-effective program of affordable health care, keeping the best interest of the patient always in mind. We should offer surgical care that is reasonably priced and, at the same time, is "high tech" and "high touch." If we, as a society, decide that we cannot afford to pay for unlimited medical care, then we must help to determine what is the maximum affordable basic level of medical care to which all citizens have a right. Since one of the largest impacts on cost containment is prevention, the leading causes of morbidity and mortality may be reduced substantially if we take strong stands to support programs against smoking, driving under the influence of alcohol, using drugs, and help educate the public with respect to good nutrition, immunization, and personal health.

We must make a commitment to find better methods for providing care for the indigent, including donating a portion of our professional time and inspiring an interest in public service among our colleagues. Community, city, county, state, and government clinics and hospitals, which provide the major portion of health care to financially underprivileged patients, require much volunteer time from almost all physicians, including surgical specialists, if we are to continue to provide the best medical care available to all our citizens.

We must participate actively in the standardization of medical and surgical fees. Being a professional requires experience and judgment, and that is where medicine may clash with corporate and government attempts at cost containment. Clinical judgment is something one learns only by practicing, although occasionally a judgment call by a physician may be regarded in the eyes of the regulators as extravagant. We must participate actively with government and health care organizations to determine the relative value of our surgical services compared with all other medical services available in providing the best available care to all citizens. This year, the Pacific Coast Surgical Association has had considerable input into the deliberations by the American College of Surgeons, as well as the government-supported Hsaio Commission's development of a resource-based relative value surgical fee schedule.

We should scrutinize and tighten the indications for all medical and surgical procedures. The operations we perform must be "necessary" for the well-being of the patient; our obligations should not cease when surgery is not the optimum therapy for an illness. We must be very aware of the high cost of medical tests and procedures and attempt to avoid using the excuse of "defensive medicine" and the availability of new technology as the indications. Considerable progress has been made in this area through the American College of Surgeons and working with the recently developed hospital quality assurance programs, but there is still much room for improvement.

We must take a strong stand to uphold competence. Although efforts by the medical profession to control those physicians who are judged to be incompetent or unprofessional by their peers have been frustrated in recent years by sanctions enjoined against medical societies, boards, and committees, under the rubric of "restraint of trade," we must tighten our peer review system. We must directly and forcefully deal with those who abuse the public trust and work together with our colleagues in the legal profession and in hospital administration. We must begin to take a more active role in determining what is an unfortunate medical outcome without negligence from that due to physician error or incompetence. The new hospital-based quality assurance programs are a step in the right direction that should be supported and guided by our medical and surgical associations. We should strive to protect quality, but also control costs; to reject the incompetent, yet nurture the excellent.

We should maintain a creative mind to continue to improve the technology and standards of our profession. We must continue to strongly support and participate actively in both basic and clinical research and to maintain an interchange of knowledge, one of the prime goals of this Association. Judicious use of new technology is imperative. One must not forget that the stethoscope can provide very helpful information, and that the computed tomography scan need not always be part of the initial examination. We must further realize that medical knowledge and experience are for our patient's benefit, and are not commodities that are for sale.

Most important, we must maintain a deep sense of compassion with personal concern for our patients' overall well-being, as well as for their medical treatment. We must prevail in our efforts to preserve our professional ethics, ideals, and humanism in patient care, for nothing we could possibly do would help more to restore the loss of public trust and confidence and enhance our continuing privilege of being considered professionals.

COMMENT

This past summer my wife and I were privileged to take a cruise through the beautiful Alaskan waterways. The captain of the ship steered us through iceberg-filled fjords, assisted by the latest computerized technology and pilots, the course chosen based on his judgment and experience. He held the trust and confidence of all passengers, perhaps one of the last vestiges of independent decision making in a public setting. Surgeons have often been accorded the title "captain of the ship" since they have the trust and confidence of their patients while making independent decisions based on judgment and experience. The surgeon of today and tomorrow must care about more than making the correct diagnosis and proceeding with an expeditious and accurate operation using state-of-the-art technology. He or she must maintain a humanistic relationship with the patient and the patient's family, for holding the trust of others as a professional is a privilege that carries broad responsibilities.

In closing, may I express the hope that my feelings of optimism and confidence are shared by other surgeons. I have tried to share with you some of my sincere concerns, convictions, and constructive responses. The future of surgical care is challenging, and the Pacific Coast Surgical Association must continue to play a major supporting role in that future. We must address, identify, and stand up for, as an organization and as individuals, what is sound and sensible about the future practice of medicine. I have the utmost trust that regardless of the changes in the system under which we practice, surgeons will strive to provide nothing short of the best technical and humanistic patient care with an increasing dedication toward working to a solution of the large number of medical and social issues at hand.

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Is Arterial Proximity a Valid Indication for Arteriography in Penetrating Extremity Trauma?

A Prospective Analysis

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• Three hundred seventy-three patients with a penetrating extremity injury were studied to assess the yield of arteriography. Patients underwent arteriography if any of the following was present: bruit, history of hemorrhage or hypotension, fracture, hematoma, decreased capillary refill, major soft-tissue injury, or nerve or pulse deficit. In the absence of these findings, arteriography was performed if the injury was in "proximity" to a major neurovascular bundle. In 216 patients, arteriography was performed when an abnormal finding was noted. Sixty-five injuries were identified, 19 requiring intervention. Proximity was the indication for arteriography in 157 patients. Seventeen injuries were identified, of which one required repair. In penetrating extremity trauma, the need for arteriography is based on clinical findings. The use of arteriography to screen for an arterial injury when proximity alone is the indication rarely identifies a significant injury and should be abandoned.

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Rather than risk the medical and possible legal consequences of a missed arterial injury, it has become common practice for surgeons to employ arteriography as a screening device in patients with penetrating extremity trauma. The value of arteriography in patients who do not require immediate operative intervention but have obvious signs of an arterial injury, is readily apparent. An arteriogram performed in either the operating room or radiology suite will identify the location and nature of an injury and assist in planning the subsequent treatment. The value of arteriography in patients in whom there are no definite signs of an arterial injury is less clear. The recognition that occult arterial injuries may be present despite the absence of overt physical signs of arterial trauma has led many surgeons to advocate the routine use of diagnostic arteriography for injuries in "proximity" to a major neurovascular bundle.[1-7]

The clinical usefulness and diagnostic yield of arteriography for penetrating extremity injuries in proximity to a neurovascular bundle remains controversial. A recent report by Frykberg et al[8] suggests that the ultimate benefit of routine arteriograms is minimal and represents overuse of costly medical resources. Others, however, have maintained that if arteriography for proximity were abandoned, major arterial injuries would be missed. This would result in serious medical, legal, and financial consequences.[4,8,9] This study was designed to address these concerns by prospectively determining the diagnostic and therapeutic yield of arteriography when routinely performed for proximity alone as well as for other signs more directly suggestive of an arterial injury.

PATIENTS AND METHODS

During the 18-month period from July 1, 1987, to December 31, 1988, 373 patients with a unilateral penetrating injury to an upper or lower extremity were entered into a prospective study designed to assess the value of routine diagnostic arteriography in identifying clinically occult arterial injuries. Patients with a penetrating injury distal to the deltopectoral groove or inguinal ligament underwent arteriography if a distal pulse deficit, nerve deficit, hematoma, history of hemorrhage or hypotension, bruit, fracture, major soft-tissue injury, or delayed capillary refill was present; or if in the absence of these findings, the path of the penetrating object was judged by the admitting surgeon to be in proximity to a major neurovascular bundle. All arteriograms were performed in the radiology department via a femoral puncture and confined to the injured limb. Patients with bilateral penetrating injuries, injuries outside the defined anatomic boundaries, or arterial injuries that required operation because of severe limb ischemia or active hemorrhage were excluded.

Before the arteriogram was performed, information on the age and sex of each patient, injury type (stab wound, shotgun wound, gunshot wound, or other), extremity injured (arm or leg), and side injured (left or right) was obtained. A history of hemorrhage or hypotension, the quadrants (medial anterior, medial posterior, lateral anterior, and lateral posterior) traversed by the penetrating object, and the presence of a bruit, pulse deficit, hematoma, fracture, major soft-tissue injury, neurologic deficit (sensory, motor, combined, or glove distribution), or decreased capillary refill was noted. In 210 patients, posterior tibial/dorsalis pedis or radial/ulna Doppler pressures of the injured and contralateral uninjured extremity were obtained and indexed (ankle-arm/brachial index [ABI]) using the brachial Doppler pressure of an uninjured extremity.

Each arteriogram was interpreted as "normal" or "injured." The arterial segment injured was described. Arterial injuries were defined as "major" or "minor." Major injuries were injuries to arterial segments that, if interrupted, would likely result in clinically significant limb ischemia. All other arterial injuries were termed *minor.* The arterial injury was further classified as an intimal defect, intimal flap, pseudoaneurysm, arteriovenous fistula, stenosis, or occlusion as defined in a previous report.[10] Therapy was based on the arteriographic findings and included observation, arteriographic embolization, arterial ligation, or repair.

The arteriographic findings, arterial segment injured, and treatment were compiled for patients in whom diagnostic arteriography was performed for abnormal clinical findings and for patients without abnormal findings in whom proximity alone was the indication.

The sensitivity and specificity of the Doppler ABI in predicting an arteriographic arterial injury were determined for the 210 patients in whom Doppler data were available. The minimum of the two ABIs (MABI) at the ankle or wrist were used for these determinations. Three different ranges, less than or equal to 0.99 and less than or equal to 0.90, were arbitrarily chosen as abnormal for these calculations. Sensitivity represents the percent of arteriographic arterial injuries correctly predicted by an abnormal MABI and specificity represents the percent of normal arteriograms correctly predicted by a normal MABI.

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For all patients, a multivariate stepwise logistic regression analysis was performed to determine whether any abnormal findings correlated with the arteriographic demonstration of a major or minor arterial injury.[11] The following variables were considered for this analysis: age, sex, injury type, extremity, side, projectile path by quadrant, pulse deficit, fracture, major soft-tissue injury, hematoma, neurologic deficit, bruit, history of hemorrhage, hypotension, decreased capillary refill, and MABI of the injured and contralateral uninjured extremity.

Three hundred seventy-three patients were entered into the protocol; 345 were male and 28 were female. Median age was 24 years (range, 10 to 73 years). There were 229 (61%) lower and 144 (39%) upper extremity injuries. The right extremity was injured in 172 (46%) cases and the left in 201 (54%) cases. The quadrants traversed by each injury are shown in Table 1. The incidence of injury type, history of hemorrhage or hypotension, fracture, hematoma, neurologic deficit, pulse deficit, soft-tissue injury, decreased capillary refill, and bruit are found in Table 2. Two hundred sixteen patients (58%) underwent arteriography because one or more abnormal findings were present, and 157 (42%) had proximity alone as the indication.

Table 1.—Quadrants Traversed by Penetrating Injury vs Arteriographic Findings

Quadrants*	No. of Patients	Arteriographic Findings, No. Normal	Injury (%)
Med/ant-med/post	26	21	5 (19)
Med/ant-lat/ant	32	19	13 (40)
Med/ant-lat/post	34	28	6 (18)
Med/ant-no exit	113	94	19 (16)
Med/post-lat/ant	24	13	11 (46)
Med/post-lat/post	15	10	5 (33)
Med/post-no exit	29	26	3 (10)
Lat/ant-lat/post	6	6	0
Lat/ant-no exit	56	44	12 (21)
Lat/post-no exit	40	31	9 (22)
Total	**373**	**291**	**82**

*Ant indicates anterior; Lat, lateral; Med, medial; and Post, posterior.

Table 2.—Incidence of Arterial Injury for Each Injury Type or Abnormal Finding

	No. of Patients	Arterial Injury, No. (%)
Injury		
Stab wound	79	13 (16)
Shotgun	24	11 (46)
Gunshot	256	57 (22)
Other	13	1 (8)
Fracture	95	25 (26)
Hematoma	76	21 (28)
Neurologic deficit		
Sensory	27	14 (52)
Motor	13	3 (2)
Motor/sensory	22	8 (36)
Glove	1	0
All	63	25 (40)
Pulse deficit	38	22 (56)
Soft-tissue injury	19	4 (21)
Hemorrhage history	10	2 (20)
Decreased refill	8	3 (38)
Hypotension	4	2 (50)
Bruit	1	1 (100)

RESULTS

Eighty-two patients (22%) had an arterial injury demonstrated arteriographically (Table 3). The quadrants traversed by the penetrating object and the incidence of arteriographic injuries for each combination are found in Table 1. The incidence of a positive arteriogram for given injury or abnormal finding is found in Table 2. The mean and median MABI in extremities with an arterial injury were 0.81 and 0.92, respectively. In extremities in which an arterial injury was not demonstrated, the mean MABI was 0.94 and the median, 0.99. The sensitivity/specificity of the MABI in predicting an arterial injury was 82%/40% at less than or equal to 0.99, 71%/63% at less than or equal to 0.95, and 49%/76% at less than or equal to 0.90.

In the 216 patients with abnormal findings, 65 arterial injuries were found, of which 22 were major and 43 were minor. Nineteen injuries in this cohort required arterial repair or embolization. Proximity alone was the indication for arteriography in 157 patients. In this group, 17 arterial injuries (four major and 13 minor) were demonstrated. One injured artery underwent ligation (Table 3).

Overall, 20 arterial injuries were treated by repair or arteriographic embolization. The arterial repair was end-to-end in 11 and by vein interposition in four. Embolization was performed for four injuries and arterial ligation for one. All other injuries were treated nonoperatively. The major artery injuries treated nonoperatively included intimal defects (n = 7), occlusions (two profunda femoris, one profunda brachii) (n = 3), pseudoaneurysm (n = 1), and stenosis (n = 1). Thirty-two minor artery occlusions, five intimal defects, five intimal flaps, five small pseudoaneurysms, and three small arteriovenous fistulae were treated nonoperatively (Table 3).

Following arterial repair, all patients were discharged with a patent repair and intact vascular examination. Embolizations were successful in all instances. No untoward events occurred in those patients treated nonoperatively and all were discharged with a stable vascular examination and intact limb.

Twenty-one patients treated nonoperatively have been followed up from 1 to 8 months (median, 2 months) after injury and remain clinically stable. Ten patients have undergone repeated arteriography at 4 days to 2 months after injury to reassess five intimal injuries, three arteriovenous fistulae, and two pseudoaneurysms. All injuries had resolved with the exception of an intimal defect in the radial artery, which was unchanged, and a persistent medial geniculate arteriovenous fistula, which was embolized.

For the stepwise logistic regression analysis, the following variables were initially considered for the model: age, sex, injury type, extremity, side, distal pulse deficit, fracture, major soft-tissue injury, hematoma, neurologic deficit, bruit, history of hemorrhage, hypotension, and decreased capillary refill. Those variables that occurred in less than 10 patients, ie, bruit, history of hemorrhage, hypotension, and decreased capillary refill, were subsequently not entered. A pulse deficit, neurologic deficit, and shotgun injury were shown to correlate significantly ($P < .05$) with arteriographic evidence of an arterial (major or minor) injury. The presence of one or more of these variables identified a high-risk group of 104 patients. Forty patients in this group had an arterial injury, a yield of 38%. Fifteen of the 40 patients with an arterial injury required arterial repair or embolization; 25 were observed.

The remaining cohort of 269 patients had none of these high-risk predictors. A second stepwise logistic regression analysis was performed using these 269 patients, the above variables, and the same end point of arteriographic injury. Also entered in this regression analysis were the MABI of the

Table 3.—Arteriographic Findings and Treatment*

	AG Indication		AG Findings						Treatment			
Artery	Findings	Proximity	Defect	Flap	Panysm	Sten	Occl	AVF	Repair	Embol	Ligate	Observe
Major												
Brachial	9	1	1	...	2	2	5	...	7	...	...	3
Profunda brachii	...	1	...	...	...	...	1	...	...	...	...	1
Femoral												
common	1	...	...	1	...	...	...	...	1	...	...	...
Superficial	6	...	4	...	2	...	...	...	2	...	...	4
Profunda	2	2	1	...	1	...	2	...	...	1	...	3
Popliteal	4	...	1	...	...	...	2	1	3	...	...	1
Minor												
Tibial/ulnar/radial	31	6	3	5	5	...	22	2	2	3	1	31
Branch	12	7	2	...	3	...	12	2	...	...	...	19
Total	**65**	**17**	**12**	**6**	**13**	**2**	**44**	**5**	**15**	**4**	**1**	**62**

*AG indicates arteriogram; AVF, arteriovenous fistula; Embol, embolization; Occl, occlusion; Panysm, pseudoaneurysm; Sten, stenosis.

injured and uninjured extremity, and a new variable, "soft." The MABI of the injured extremity was considered positive if less than or equal to 0.99 or less than 0.10 of the uninjured extremity MABI. All patients in whom MABI was not available were included in the analysis with MABI coded as unknown. Soft was constructed as positive if a fracture, hematoma, bruit, decreased capillary refill, history of hemorrhage, hypotension, or soft-tissue injury was associated with the penetrating injury. In this cohort, an MABI less than or equal to 0.99 and the variable soft were significantly ($P<.05$) correlated with an arterial injury. Either one or both of these variables were present in 165 patients and represented an intermediate risk group. Thirty-three patients (20%) had an arterial injury, five of which required intervention.

A low-risk group of 104 patients with none of the above findings remained. Nine injuries (9%) (one profunda brachii occlusion, one profunda femoris occlusion, one brachial intimal defect, one profunda femoris intimal defect, and five branch occlusions) were demonstrated arteriographically in this group. In seven of the nine patients with injuries, Doppler data were not available. The stratification of the arterial injuries and treatment for the three risk groups is found in the Figure.

To investigate whether a specific projectile path might correlate with the presence of an arterial injury, the quadrants traversed by the penetrating injury (Table 1) in patients with a thigh or upper arm injury were analyzed by stepwise logistic regression. A significant correlation ($P<.05$) was found for a projectile path traversing the medial posterior and lateral anterior quadrants. In nine patients, this path was present in the absence of one or more of the significant variables (pulse deficit, nerve deficit, shotgun injury, MABI less than or equal to 0.99, and soft). Two arterial injuries, a profunda femoris intimal defect, and a branch occlusion were found in these nine patients.

COMMENT

The evolution of arterial reconstruction during World War II and the Korean War incorporated a policy of mandatory surgical exploration for all penetrating wounds in proximity to major vascular structures.[12] Concurrently, mandatory exploration of extremity wounds in proximity to a major neurovascular bundle became accepted practice in the management of civilian trauma.[7,13,14] This policy, although resulting in a decrease in missed arterial injuries, resulted in a large number of surgical explorations in which no arterial injury was identified. Refinements in the safety, availability, and resolution of contrast arteriography provided a diagnostic modality that accurately screened for arterial trauma in patients with proximity injuries and eliminated the need for surgical exploration.[3,5] The value of this diagnostic approach in penetrating trauma rapidly became apparent and routine arteriography for proximity wounds soon became common.

Initially, clinically occult arterial injuries were reportedly identified by arteriography in up to 20% of patients.[15] Because the natural history of these injuries was difficult to establish, there was appropriate concern that, if untreated, these injuries would invariably result in arterial thrombosis, hemorrhage, or aneurysm formation. Consequently, all injuries in major vessels identified arteriographically were explored and repaired.

In recent years these practices have come under increased scrutiny for the following reasons:

1. The yield of abnormal arteriograms in patients in whom proximity is the arteriographic indication may be less than 10%, not the 20% reported earlier.[3]
2. The concept of proximity is ambiguous and, depending on the surgeon, may be interpreted in a variety of ways, often resulting in inappropriate utilization of diagnostic arteriography.
3. Arteriograms are less than perfect. A low but real incidence of false-negative arteriograms has been demonstrated experimentally as well as clinically and a 2% incidence of false-positive arteriograms has also been reported.[4,5,16,17]
4. Arteriography is an expensive screening modality. Depending on the institution, the cost of a single negative screening arteriogram can range from $750 to $1500.[8]
5. In addition to the cost of negative studies, serious arteriographic complications can occur. Although the incidence of arteriographic complications in our institution has been exceedingly low, Reid et al[9] reported a 2.6% incidence of complications following extremity arteriograms performed for proximity.
6. The majority of injuries identified by arteriography in otherwise asymptomatic patients are, in most instances, small intimal defects, small pseudoaneurysms, or occlusions of noncritical vessels. Previously, these injuries were all operated on; however, it has been recently demonstrated that the great majority of these injuries heal spontaneously with few sequelae.[9,18]

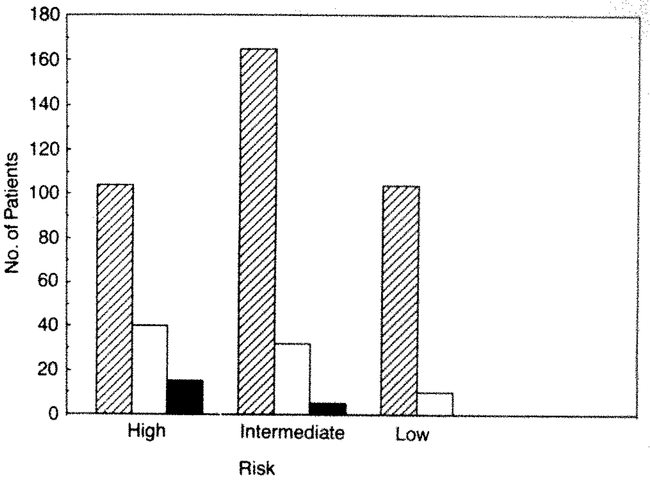
This reasoning suggests that a policy of routine arteriography for proximity alone may be of minimal clinical benefit and an inefficient use of medical resources. This study we thus designed our study with the following two purposes: first, to ascertain prospectively the practical yield of diagnostic arteriography when routinely employed for proximity alone and to determine, for a given finding or constellation of clinical findings, the risk of arterial injury following a penetrating injury to an extremity; and second, to investigate the usefulness of Doppler pressure measurements, a noninvasive, inexpensive modality, as an alternative screening test for clinically occult arterial injuries.

The indication of proximity alone was attended by an arteriographic finding of an arterial injury in 11% of patients, similar to other recent reports.[3,9] Only four (2.5%) of these injuries were of major arteries, all profunda brachii or femoris, none of which required surgical intervention. Ligation of a small pseudoaneurysm of the ulnar artery was the only operation required. Given our more recent experience with selective management of minimal nonocclusive injuries, we would not at this time initially treat this injury surgically.[10] In contrast to these findings, 65 arterial injuries, 22 of which were major, were detected arteriographically in 216 patients with one or more abnormal findings. Nineteen of these injuries required operation or embolization.

Clearly, the presence of one or more abnormal findings resulted in an increased diagnostic yield compared with proximity alone. To better define what specific demographic, injury, or abnormal clinical findings might correlate with an arterial injury, the statistical method of stepwise logistic regression was used. In decreasing order of significance, a pulse deficit, neurologic deficit, and shotgun injury defined a high-risk group of 104 patients. The presence of one or more of these findings was found in 49% of the patients with arterial injuries and 75% of patients with injuries requiring repair. As one would expect, a pulse deficit was the most predictive of an arterial injury. However, of more interest is the finding that the presence of a neurologic deficit and shotgun injury were correlated as well. With one exception, the neurologic deficits identified in this study corresponded to specific motor and sensory pathways that travel with the major arterial trunks, confirming the value of a careful neurologic examination in the evaluation of penetrating extremity trauma. The strongly positive correlation of shotgun injuries is in agreement with the high prevalence of arterial injuries documented by Frykberg et al[8] following a shotgun injury, and is most likely due to the multiple pellets and wide anatomic scatter of these injuries.

Excluding those patients with one or more of the high-risk findings, a second analysis, in which the remaining variables were entered, was performed. A new variable soft was constructed and entered into this analysis to determine the combined predictive value of the remaining abnormal findings. In addition, hemodynamic data and quadrant location were incorporated into the model to determine their potential predictive value. The data pertaining to quadrant location were obtained and entered in an attempt to objectively assess the validity of proximity as an indication for arteriography. Although none of the remaining abnormal clinical findings was individually correlated with an arterial injury, taken as a group, they were significantly correlated. The importance of an MABI less than or equal to 0.99 as a predictor of arterial injury was evident as well.

Others have proposed that Doppler pressure measurements may be of value in the management of penetrating extremity trauma, and the decreased mean and median MABI in patients with an arterial injury compared with those without an injury supports this contention.[2,8] However, there are minimal data correlating a specific ABI with an arterial injury. We therefore selected three arbitrary ranges and defined them as abnormal in an attempt to determine the ABI value that would provide the optimum sensitivity and specificity. When defining an abnormal MABI as less than or equal to 0.99, the MABI was sufficiently sensitive to predict over 80% of the arterial injuries, but at the expense of a very low specificity. Lowering this threshold to those of less than or equal to 0.95 and less than or equal to 0.90 markedly decreased the sensitivity of the MABI. These data suggest that Doppler measurements may be useful in guiding the need for arteriography. Further studies to better define the diagnostic limits of Doppler measurements should be pursued.



Bar graph depicting high-, intermediate-, and low-risk patient groups as determined by the stepwise logistic regression analysis. The arterial injuries and operations/embolizations required are graphically illustrated for each group. Shaded bars indicate patients; open bars, arterial injury; and solid bars, operation/embolization.

A second or intermediate risk group of 165 patients was identified by the presence of either the soft variable or an MABI less than or equal to 0.99 or both. This group encompassed 33 arterial injuries and the remaining five operations or embolizations not identified in the high-risk group.

The finding that a projectile path traversing the medial posterior and lateral anterior quadrants in the upper arm or thigh was correlated with an arterial injury added little to the identification of patients at risk for an arterial injury. Excluding those patients already identified by the above significant variables, this projectile path was present in only nine patients, two of whom had minimal arterial injuries. Other paths that were potentially in proximity to the course of a major neurovascular bundle were not found to be independently correlated with an arterial injury.

The low-risk group comprised patients who did not manifest any abnormal clinical findings and had an MABI greater than or equal to 1. All patients in this group had arteriograms for proximity. Nine injuries were identified, but none required any intervention. Data from our group as well as Stain et al[10] and Frykberg et al[18] suggest that the injuries detected in this group have a clinically benign natural history.

A policy of performing arteriography exclusively for intermediate and high-risk groups and eliminating proximity as an indication would have identified 89% of injuries and 100% of injuries that required intervention. Nearly a third of the arteriograms performed in this study would not have been performed without significant risk to a single patient.

This prospective study confirms that proximity alone is an insufficient indication for diagnostic arteriography in penetrating extremity trauma, since the yield is low and the necessity for operation infrequent. The need for arteriography can be more precisely based on a careful clinical examination and readily available noninvasive testing. Furthermore, this experience suggests that significant arterial injuries

manifest abnormal clinical findings or objective hemodynamic evidence of arterial compromise, making a more selective application of arteriography in the evaluation of the traumatized limb practical and safe.

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Discussion

KAJ JOHANSEN, MD, Seattle, Wash: The traumatized limb that potentially harbors an occult vascular injury represents a diagnostic and management dilemma.

This study is the latest and most important nail in the coffin of the routine or "exclusion" arteriogram for the limb potentially harboring a silent arterial injury. Recent work from the Universities of Florida, Dallas, Denver, and Southern California has documented that such arteriograms are expensive, invasive, and have an significant incidences of false-positive and false-negative results; are mostly unrevealing of arterial damage; and in the majority, discover abnormalities that are clinically irrelevant. These studies continue to be performed because of a combination of diagnostic inertia and "litigation phobia."

In this study, the authors suggest that factors that can easily be determined by history and physical examination actually can make a clinical difference. Second, through the means of multivariate stepwise logistic regression analysis, they stratify their patients into high-, intermediate-, and low-risk categories; the first, based on the presence of a shotgun injury by history, pulse, or neurologic deficit on examination; the second, based on a constellation of physical, hemodynamic, and anatomic findings; and the third, based on proximity alone in the absence of any other worrisome clinical data.

My first observation is based on the shortcomings of an epidemiologic study in providing guidance for the individual patient. Using what we term the *arterial pressure index* (arterial pressure of injured limb divided by arterial pressure in an uninvolved arm), and setting normal at greater than 0.90, we have found a negative predictive value of 99% for Doppler pressure measurement in this setting. At Harborview, we have completed a prospective study in which arteriography was performed only for limbs with an arterial pressure index less than 0.90. We had no missed injuries and a 94% likelihood of positive findings in those patients who *did* undergo arteriographic studies, and reduced the number of extremity angiograms by fourfifths.

My questions are as follows: (1) This study examined penetrating injuries only. Do you have data for blunt trauma as well? Do you have any reason to believe your conclusions would be different in that setting? (2) If arteriograms are to be used as the "gold standard," we must agree that they are only 14-karat gold. What was the incidence of misleading arteriogram results in your series? (3) Young, healthy arteries go into spasm very readily. You do not report it as an angiographic finding; can you explain this? (4) Finally, the greatest expense of performing arteriography in the trauma patient is that of the time expended: in our center, a mean of 2.4 hours. How long does your average study take?

F. WILLIAM BLAISDELL, MD, Sacramento, Calif: I take issue with two aspects of this study. First, there was a significant incidence (11%) of injury in the wound of proximity group. Although it was stated that only one of these patients required surgical treatment, the problem with this group is that they are unreliable. They do not come back for follow-up, so you have to resolve the problem initially: do they have an injury or not?

The second issue is that while physical examination is all-important and the use of the vascular laboratory has increased our diagnostic acumen, the definitive study is arteriography. The principal arguments against arteriography are the time and expense required to do it.

Initially, surgeons did their own arteriography, and I believe more should be done by us either in the operating room or in the emergency department This markedly decreases the time and expense of the procedure and yields definitive information immediately.

If a patient has evidence of injury, he or she should to be taken to the operating room without any delay. If arterial wound is not certain, ie, if it is a shotgun wound, an arteriogram can be obtained at the time of surgery. Minimizing the time delay between injury and operation is key to getting the optimal result in the management of vascular injury, and we should be doing arteriography ourselves in this group of cases.

DR YELLIN: We are suggesting that the physical examination might often replace the routine arteriogram for proximity trauma. It is important for us to question and reexamine old concepts, particularly in the light of new knowledge. We have discarded routine surgical exploration for penetrating trauma; perhaps the same will be true for proximity arteriography. Proximity arteriography is not perfect. There are false positives, false negatives, complications, and considerable economic costs.

Our data and those of Dr Johansen have demonstrated that clinical findings and the ankle brachial index can predict which cohort of patients requires arteriography. Essentially 100% of clinically relevant injuries, and those requiring intervention, will be identified within this group. To accept this concept one must also believe that the minor injuries that may be missed do not need operative intervention. We and others have now demonstrated this.

Dr Johansen, it takes between 1.5 and 4 hours to obtain an angiogram depending on whether it is day, night, or weekend. This affects cost. To carry on Dr Blaisdell's thoughts, however, any patient with hemorrhage or ischemia goes directly to surgery without pausing for arteriography. If necessary, a one-shot arteriogram can be obtained in the operating room. We are about to report a similar study with patients with blunt trauma, and the data are even more convincing that the physical findings are an excellent predictor of arterial injury. We have not had false-positive arteriograms confirmed by surgery (in which no arterial injury was found). We cannot be certain about false-negatives because these patients were not operated on. We have a captive population; our young warriors return to us because they have no other hospital to go to. We do not see them return with missed injuries; they return often with a second gunshot or stab wound. We had 22 patients with spasm on arteriogram. All resolved and all were classified as normal arteriograms. Had we considered these as abnormal or as positive arteriography injuries, our data would have been even more statistically significant and more relevant.

Is Liver Transplantation Justified for the Treatment of Hepatic Malignancies?

Kim M. Olthoff, MD; J. Michael Millis, MD; Michael H. Rosove, MD; Leonard I. Goldstein, MD;
Kenneth P. Ramming, MD; Ronald W. Busuttil, MD, PhD

• Twenty-eight patients received orthotopic liver transplants for malignant disease between February 1, 1984, and December 31, 1989. Preoperative diagnoses included hepatocellular carcinoma (n = 16), cholangiocarcinoma (n = 3), other primary hepatic tumors (n = 6), and metastatic diseases to the liver (n = 3). Overall actuarial survivals at 6 months, 1 year, and 5 years were 67.3%, 51%, and 31%, respectively. Long-term survival longer than 5 years was achieved in 3 patients. The recurrence rate in patients surviving longer than 3 months is 48% (median, 7 months). Hepatocellular carcinoma and cholangiocarcinoma had the poorest survival and highest recurrence rates. Specific prognostic factors correlating with survival or recurrence could not be elucidated. These results indicate that orthotopic liver transplants can provide long-term cure and palliation for malignant disease; however, patient selection is extremely important in predicting outcome.

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In the early evolution of orthotopic liver transplantation (OLT), unresectable malignant disease confined to the liver was initially believed to be an excellent indication. Many of the early successes in liver transplantation were obtained in patients with hepatic tumors unresectable by standard methods, and early survival was equal to, if not better than, those patients with benign liver disease.[1] As follow-up extended beyond the early postoperative months, it soon became apparent that tumor recurrence occurred frequently, often in the first 2 years following transplantation.[2] With continued improvements in operative technique, immunosuppression, and intensive care, it was no longer the technical expertise and the ability to perform the procedure with acceptable morbidity and mortality that determined long-term outcome of tumor patients, but careful patient screening and selection.

The appropriateness of performing OLT for malignancy has been questioned in recent years as several centers began to report disappointing survival statistics and high recurrence rates.[3] The question arises, should we transplant a limited resource of donor livers into patients who have a significant rate of early recurrence and a much lower survival rate than those who underwent transplantation for end-stage benign liver disease? Alternatively, can we cease performing a procedure that offers the only possibility of cure in these patients? Finally, how can we select those patients who have the best chance of long-term survival?

To answer these questions and determine if OLT is justified for the treatment of hepatic malignancies, we performed a retrospective analysis of our experience with OLT for malignant disease and reviewed the recent results of many of the larger transplant centers in North America and Europe.

PATIENTS AND METHODS

At UCLA, we performed 492 OLTs in 413 patients between February 1984 and December 1989. Of these, 28 patients underwent transplantation for malignant disease; 16 patients had primary hepatocellular carcinoma (HCC), including one of the fibrolamellar type; three were diagnosed with cholangiocarcinoma; and six had other primary hepatic tumors including hemangioendothelioma (n = 3), neurosarcoma (n = 1), lymphangioma (n = 1), and hepatoblastoma (n = 1). Three patients had nonhepatic primary tumors that had spread to the liver: one leiomyosarcoma from the stomach, one metastatic pancreatic adenocarcinoma, and one metastatic islet cell tumor (Tables 1 and 2). Incidental carcinomas were not included in this analysis.

Of the 28 patients, 15 were female and 13 were male. The ages of the patients ranged from 2 to 70 years (mean, 36.6 ± 18.4 years), five of whom were less than 16 years old, four were between ages 16 and 30 years, 15 were between ages 31 to 50 years, and four were older than 50 years.

All patients were evaluated extensively prior to OLT, with the exception of one patient (No. 129) who was transferred in acute fulminant hepatic failure. Preoperative evaluation of all patients with tumor included history, physical examination, and laboratory studies (including liver function test, measurement of α-fetoprotein and carcinoembryonic antigen, and serologic analysis). Abdominal ultrasound, chest and abdominal computed tomographic (CT) scan, bone scan, and angiography were routine preoperative studies, and exploratory laparotomy was performed in three patients prior to OLT. Eleven patients received chemotherapy prior to transplantation.

Orthotopic liver transplantation was performed by conventional techniques as previously described,[4] except in two patients with metastatic pancreatic neoplasms who underwent foregut resections in combination with hepatic replacement. Furthermore, in performing the recipient hepatectomy, attention was paid to excising all

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Table 1.—Diagnoses and Outcomes of Patients Who Underwent Orthotopic Liver Transplantation (OLT)

Patient No.	Diagnosis	Date of OLT	Outcome	Follow-up, mo
1	Neurosarcoma	2/1/84	Dead	4
2	Metastatic leiomyosarcoma	3/20/84	Alive	70
4	Hepatoma	5/11/84	Dead	1
6	Hepatoblastoma	6/11/84	Alive	67
9	Hemangioendothelioma	8/8/84	Alive	65
11	Hepatoma/tyrosinemia	8/30/84	Dead	10
18	Cholangiocarcinoma	2/4/85	Dead	22
28	Hepatoma	5/16/85	Dead	10
64	Hepatoma	6/5/86	Dead	31
81	Hemangioendothelioma	10/5/86	Alive	39
97	Hepatoma	1/9/87	Dead	15
125	Lymphangioma	6/11/87	Alive	31
129	Hepatoma	6/25/87	Dead	3*
160	Hepatoma	10/20/87	Alive	26
164	Hepatoma	10/28/87	Dead	5
178	Hepatoma	12/24/87	Dead	21.5
211	Hemangioendothelioma	3/21/88	Alive	21
223	Hepatoma	4/26/88	Dead	2*
225	Hepatoma	5/1/88	Alive	20
227	Cholangiocarcinoma	5/5/88	Dead	8
249	Hepatoma	7/18/88	Dead	6
259	Hepatoma	8/25/88	Dead	5
265	Cholangiocarcinoma IVC thrombosis	9/14/88	Dead	1
283	Hepatoma	11/5/88	Dead	5
309	Hepatoma	2/13/89	Alive	11
334	Metastatic pancreatic adenocarcinoma	4/29/89	Dead	4.5
347	Hepatoma	6/9/89	Dead	3*
371	Metastatic islet cell neuroendocrine tumor	8/10/89	Alive	5

*Follow-up period was 3 days for patient 129; 2 weeks for patient 223; and 3 weeks for patient 347.

Table 2.—Histologic Features of 28 Hepatic Tumors

	No. of Patients
Primary hepatic tumors	
Hepatocellular	
Fibrolamellar	1
Nonfibrolamellar	
Cirrhotic	12
Noncirrhotic	3
HepBSAg +	6
HepBSAg −	9
Cholangiocarcinoma	
Associated with sclerosing cholangitis	2
Associated with IVC thrombosis*	1
Hemangioendothelioma	3
Lymphangioma	1
Hepatic neurosarcoma	1
Hepatoblastoma	1
Metastatic tumors to liver	
Pancreatic carcinoma	
Islet cell neuroendocrine	1
Pancreatic adenocarcinoma	1
Gastric leiomyosarcoma	1

*IVC indicates inferior vena cava.

lymph node–bearing tissue around the portahepatis, gastrocolic ligament, and retrohepatic vena cava, and a short segment of recipient portal vein was left in place. Roux-en-Y choledochojejunostomy was performed in most cases. All patients received similar postoperative immunosuppression including cyclosporine, azathioprine, and prednisolone phosphate. Patients with OLT performed after 1986 also received OKT3 either prophylactically or for acute rejection.[5]

Three patients required retransplantation, one at 2 weeks due to an ischemic liver, another at 10 days for acute rejection, and another at 8 months with liver failure secondary to vanishing bile duct syndrome. Twelve patients received postoperative chemotherapy, five of these receiving therapy only after a recurrence had occurred. One patient was placed on a protocol requiring 6 months of postoperative therapy that included continuous 5-fluorouracil infusion in combination with doxorubicin hydrochloride and cisplatin administered every 3 weeks. Patients were followed up closely by CT scans and chest roentgenographs, and α-fetoprotein and carcinoembryonic antigen levels (if applicable) were monitored.

A retrospective analysis was performed obtaining information on preoperative therapy, findings at laparotomy, margins of surgical specimen, tumor size and number, presence of pseudocapsule and circumscribed tumor, histologic classification, vascular and serosal invasion, and nodal status. Data were also obtained regarding timing of recurrence and location of metastases. Deaths occurring in the first 3 months following transplantation were attributed to complications of OLT. Statistics were calculated using Kaplan-Meier cumulative survival curves and Student's *t* test.

RESULTS

Primary HCC

Sixteen patients underwent transplantation for primary HCC. Twelve had associated cirrhosis and six were associated with hepatitis B surface antigen +. One of the pediatric patients had HCC in association with tyrosinemia-related cirrhosis. Of these 16 patients, three remained alive 11, 20, and 26 months following OLT. All were in good health and free of disease. Actuarial survivals at 6 months, 1 year, and 2 years were 62.5%, 40.4%, and 22.5%, respectively. Our longest survivor in the HCC group died 31.4 months following OLT from recurrent disease.

Five patients received various courses of preoperative systemic chemotherapy. Two others were treated with preoperative chemoembolization and hepatic artery infusion of doxorubicin hydrochloride (Adriamycin). All seven of these patients died. Mean follow-up was 12.8 ± 3.9 months, which is not significantly improved over those patients who did not receive chemotherapy ($P > .05$).

Tumor size ranged from 0.5 to 15 cm and all patients had multiple tumors. The patient with the largest tumor nodule (15 × 11 × 8 cm) was still alive 26 months after OLT. There were positive lymph nodes in three of the 16 patients and vascular invasion in seven. Seven patients were found to have extrahepatic disease that was resected en bloc at the time of OLT. Only one of these patients was free of tumor longer than 6 months after OLT.

All surgical margins were negative except in one patient who arrived in hepatic coma and underwent an urgent OLT although the extent of disease was not known until laparotomy. Histologic examination revealed occult cholangiocarcinoma as well. This patient died 3 days postoperatively of multiorgan failure.

Four patients died in the first 3 months from complications of OLT including sepsis, anoxic brain death, arrhythmias, and multiorgan failure. Of the remaining patients who survived more than 3 months, eight (67%) developed recurrent disease diagnosed 2 months to 2 years following transplantation. The majority recurred in the first year (n = 5). Tumor recurrence accounted for 78% of the deaths occurring after 3 months (seven of nine patients); the other deaths were due to recurrent hepatitis and sepsis. The location of the initial tumor recurrence was the lung in four patients, the transplanted liver in two patients, and the peritoneum and chest in one patient.

The presence of cirrhosis, HepBSAg + serologic analyses, tumor size or number, vascular or serosal invasion, or the presence of positive hilar nodes has shown no significant effect on tumor recurrence or survival; however, the numbers are too small for statistical analysis. All three surviving patients and all patients who did not develop recurrence had well-circumscribed tumors, as opposed to only two in the group that did recur.

The one patient with fibrolamellar variant of HCC was doing well 11 months after OLT. She received 6 months of continuous 5-fluorouracil infusion and doxorubicin and cisplatin per an adjuvant protocol adopted in 1988. This patient required retransplantation at 8 months for hepatic failure secondary to vanishing bile duct syndrome. Her second liver is currently functioning well, and there is no evidence of recurrent disease.

Cholangiocarcinoma

Three patients in our series were found to have cholangiocarcinoma. None had a definitive preoperative diagnosis. Two patients had sclerosing cholangitis as their primary indication for OLT, but bile duct tumor was suspected. One patient was found to have a mucinous adenocarcinoma in the extrahepatic bile ducts invading the hilum. Tumor recurrence occurred in the transplanted liver 1 year 10 months after OLT. Another patient with cholangiocarcinoma associated with sclerosing cholangitis had a recurrence of disseminated metastases at 6 months. The third patient was found to have inferior vena cava thrombosis extending into the right atrium. The tumor and thrombus was resected in its entirety with clear surgical margins. Final pathologic diagnosis revealed adenocarcinoma consistent with cholangiocarcinoma, although HCC could not be ruled out. The patient died of sepsis and multiorgan failure 1 month following OLT. There was no residual disease found at autopsy. All three of these patients demonstrated vascular invasion on the pathology specimens.

Other Primary Liver Tumors

One patient with hepatoblastoma (juvenile hepatoma) underwent transplantation at age 2 years for a large 15 × 10-cm single tumor nodule. There was no evidence of extrahepatic disease and the child remained alive over 5.5 years following transplantation.

There were three cases of epithelioid hemangioendothelioma. All three remained alive and free of disease at 21, 39, and 65 months following transplantation. All three tumors consisted of multiple small tumors throughout the liver parenchyma. On microscopic inspection, one patient was found to have positive lymph nodes and vascular invasion. Another patient underwent transplantation for a lymphangioma weighing 35 pounds that filled the entire liver. She was found to have vascular and serosal invasion, but was free of recurrent disease 31 months after OLT.

The first OLT was performed in a man with a malignant hepatic neurosarcoma of the undifferentiated spindle cell type. This patient received doxorubicin and hyperthermia treatments prior to OLT. At operation, surgical margins were free of tumor and there was no lymph node or vascular invasion. However, tumor recurred at 3 months and he died 4 months following transplantation.

Of the six patients who underwent transplantation for nonhepatocellular primary liver tumors, five remained alive and free of disease with a follow-up of 21 to 67 months after OLT.

Metastatic Disease

We performed OLT for hepatic metastases of primary tumors of nonhepatic origin in three patients. Overall survival was 67% with a follow-up of 5 to 70 months.

One of the patients with metastatic disease had a primary leiomyosarcoma of the stomach that had been treated with partial gastrectomy, at which time bilobar metastases were noted. She received chemotherapy with no response and the decision was made to perform OLT. At operation, she was found to have multiple metastases ranging from 1 to 5 cm, but no extrahepatic disease. The patient was alive 70 months following transplantation without evidence of recurrent disease.

The other two metastatic tumors originated from the pancreas. Both patients had multiple metastases ranging from 0.5 to 6 cm and both had positive lymph nodes and vascular invasion. In both patients, a foregut resection was performed including total hepatectomy, pancreatectomy, partial gastrectomy, subtotal colectomy, splenectomy, and duodenectomy in a similar fashion as described by Starzl et al.[6] An OLT was completed and a gastrojejunostomy and ileocolostomy restored continuity of the gastrointestinal tract. One of these patients had a neuroendocrine islet cell tumor of foam cell histology that had studded the entire liver. She received no postoperative chemotherapy and was alive and free of disease 5 months following transplant. The other patient had a moderately differentiated pancreatic adenocarcinoma that locally invaded the diaphragm. He received fluorouracil postoperatively, but developed evidence of pulmonary recurrence 4 months following OLT.

Overall Results at UCLA

Actuarial survivals for all 28 patients at 6 months, 1 year, 2 years, and 3 years were 67.3%, 51.0%, 37.0%, and 31.0%, respectively (Fig 1). The overall recurrence rate in patients who survived longer than 3 months was 48% (median, 7 months; range, 2 to 24 months), the highest rates being in patients with HCC and cholangiocarcinoma (Fig 2). We have achieved long-term survival (more than 5 years) in several patients, as follows: 70 months after OLT for metastatic leiomyosarcoma in one patient, 67 months following OLT for hepatoblastoma in another, and 65 months following OLT for hemangioendothelioma in one other. Of the 18 patients surviving 6 months or longer, 16 (89%) returned to an active, productive lifestyle including work, homemaking, or school. We have been unable to identify any specific prognostic factors with respect to recurrence and survival in this series of patients. The presence of a well-circumscribed tumor in the patients with HCC may have a more favorable prognosis than those without, but our series is too small at this point to show any significance.

COMMENT

Orthotopic liver transplantation for hepatic malignancy remains a difficult and controversial issue. To determine the efficacy of transplant for malignant disease, it is necessary to evaluate the results of a large number of centers. In the recent years, several investigators have reported their experience with OLT for tumor: Starzl et al,[6] Iwatsuki et al,[7] Koneru et al,[8] and Koneru[9] at University of Pittsburgh, Pa; O'Grady et al[10] at Cambridge; Ringe et al[11] and Pichlmayr[3] at Hannover; Jenkins et al[12] at New England Deaconness in Boston; Flye and McCullough[13] at Washington University in St Louis; and Bismuth et al[1] reporting on the European Liver

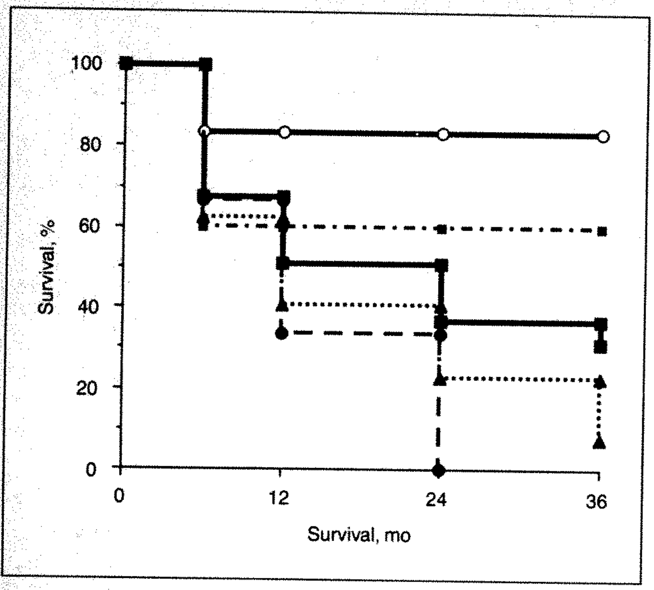

Fig 1.—Actuarial survival time vs percent after orthotopic liver transplantation for malignancy (UCLA, 1984-1989). Squares with solid line indicate overall malignancies; triangles, hepatocellular carcinoma; solid circles, cholangiocarcinoma; open circles, other primary cancers; and squares with broken line, metastatic disease.

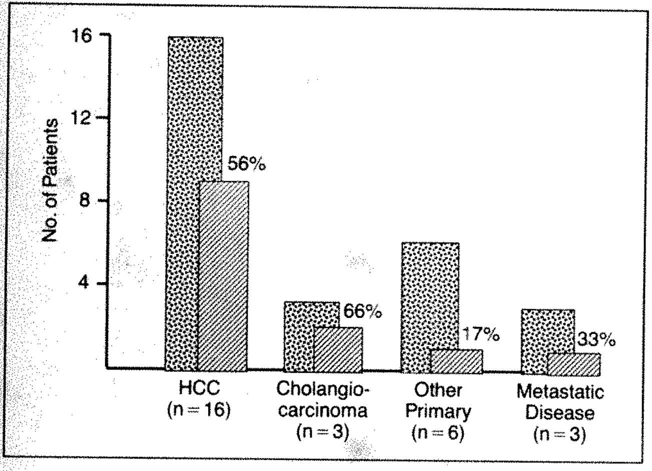

Fig 2.—Bar graph showing recurrent disease for 28 patients who underwent transplants for malignancy (UCLA, 1984-1989). HCC indicates hepatocellular carcinoma.

Transplant Registry (Table 3). Overall actuarial survival rates for all types of hepatic malignancy range from 20% to 40% at 3 years. Recurrence rates range from 37% to 65%. We will consider these centers' results according to tumor type.

HCC

Hepatic resection is the treatment of choice for primary HCC, but if the disease is bilobar or central, or if the remaining parenchyma is severely compromised from cirrhosis, subtotal hepatectomy may not be an option. Only 20% to 30% of HCCs can be considered for resection. When the HCC is unresectable, the median survival from diagnosis is only 2 to 4 months and there is no proven curative chemotherapeutic regimen to date.[14] To be considered for total hepatectomy and transplantation, a patient must have a tumor that is not amenable to partial resection by increasingly modern approaches to hepatectomy, and must demonstrate no evidence of extrahepatic spread by sophisticated preoperative studies, including laparotomy.

In the most recent series from the University of Pittsburgh,[9] 35 patients in the cyclosporine era were treated for nonfibrolamellar HCC, 14 of which were incidental carcinomas found in patients who underwent transplantation for other reasons. Of these patients, 13 were reported alive and free of disease. The remaining 21 patients underwent transplantation with malignancy as the primary indication. Sixteen patients survived more than 2 months and 56% developed recurrence. Six of the 21 patients were alive without recurrence at the time of publication. Survival at 3 years was 20%.

The fibrolamellar variant of HCC has a more favorable outcome. In general, this variant grows slower than nonfibrolamellar HCC and has a higher resectability rate.[15,16] Koneru[9] performed transplants on nine patients with this variant in the cyclosporine era, three of whom died from non–tumor-related causes. Two patients died of recurrent disease and four patients remained alive, one with recurrent disease requiring multiple pulmonary resections and chemotherapy. This patient was doing well 52 months following recurrence.

Ringe et al[11] described 52 patients who underwent transplantation for HCC (four with the fibrolamellar variant) with a 3-year survival rate of 20%. Fifty-two percent had residual disease or developed recurrent tumor. Of the 52 patients who received transplants, 15 were alive at the time of publication, one as long as 12 years. The TNM classification revealed highly significant differences in median survival time: 120 months for stage II (pT2,pN0,pM0) compared with 11.88 months for stage III and 8.75 months for stage IVA. None of the patients with lymph node metastases survived more than 1 year. Neither preoperative α-fetoprotein levels nor the

Table 3.—Review of Literature

Center	Source, y	No. of Patients	Time Span
Pittsburgh	Iwatsuki et al,[2] 1985	54	1963-1985
	Koneru et al,[8,9] 1988, 1989	71	1981-1987
	Iwatsuki et al,[7] 1989	80	1981-1989
	Starzl et al,[6] 1989	10	1988-1989
Europe (32 centers)	Bismuth et al,[1] 1987	355	1968-1987
Cambridge	O'Grady et al,[10] 1988	93	1968-1987
Hannover	Ringe et al,[11] 1989	95	1972-1987
New England Deaconess Hospital, Boston, Mass	Jenkins et al,[12] 1989	13	1983-1987
Washington University, St Louis, Mo	Flye and McCullough,[13] 1989	9	1984-1988
UCLA	Current study	28	1984-1989

presence of cirrhosis was associated with better or worse survival rates.

In the Cambridge series,[10] 50 patients with HCC, including seven with the fibrolamellar variant, received transplants. A recurrence rate of 64.9% was noted and recurrent disease accounted for 59% of the deaths after 3 months. Two-year actuarial survival was 38%. Ten of the 50 patients remained alive and there were two long-term survivors at 4.8 and 11.8 years at the time of publication. Of the patients with fibrolamellar HCC, 43% remained alive and free of disease. A longer median interval between transplant and death from recurrence was seen in patients with well-differentiated tumors.

Jenkins et al[12] reported results of transplantation performed for HCC on five patients; four of them remained alive, although follow-up was brief. In an analysis of combined results from four centers, Jenkins et al showed 1- and 2-year actuarial survival rates to be 38% and 24% for HCC (not including incidental or fibrolamellar variant). Recurrent tumor was the cause of death in 72%. The European Liver Transplant Registry, the Netherlands, a combination of 32 European centers, reported a 2-year actuarial survival rate of 30% in 217 patients who underwent transplantation for HCC.[1]

Recently, Iwatsuki et al[7] analyzed prognostic factors affecting survival and recurrence. In a group of 80 liver recipients with hepatoma vascular invasion, tumor number, tumor shape (circumscribed vs noncircumscribed), and the presence of lymph node invasion were found to be significant independent factors affecting survival. The tumor size (greater than 5 cm), multiple nodules, vascular invasion, and tumor shape (noncircumscribed) were poor prognostic histopathologic factors for recurrence in nonfibrolamellar HCC. They also confirmed that there was a longer tumor-free period in the fibrolamellar variant of HCC. In this report of 70 nonfibrolamellar and 10 fibrolamellar tumors, 1- and 3-year actuarial survival rates were 68% and 44%, respectively. Tumor recurrence rate was 37% in 68 patients who survived more than 3 months. In these patients who survived more than 3 months, tumor recurrence was the cause of death in 66%. These results show marked improvement from earlier series from the same institution.[2,8,9]

Cholangiocarcinoma

Tumors of the bile ducts appear to have a uniformly dismal prognosis at most centers. A recent Pittsburgh series reported 11 bile duct carcinomas.[9] Of the nine patients who survived more than 2 months, seven developed a recurrence and six died within 5 months of the recurrence. Only two were alive at the time of publication. None of the eight patients with bile duct carcinoma in the Cambridge series[10] survived more than 1 year. These statistics correlate with our own disappointing results with cholangiocarcinoma. Ringe et al[11] also reported sobering results with four of 10 patients with cholangiocarcinoma having extrahepatic tumor at the time of OLT. Nine of 10 patients died in less than 1 year, and one remains alive with multiple metastases. They also found the major significant influence on survival of patients with bile duct tumors to be lymph node status free of tumor. The 2-year actuarial survival rate of patients with pN0 stage was 64.1%. Patients with lymph nodes that tested positive for cancer at time of transplantation died within 1 year.

In an attempt to cure malignancies that arise from the embryonal duodenal outpouchings and eliminate their spread to foregut derivatives, Starzl et al[6] performed radical excision of the foregut and transplanted organ cluster grafts including liver, pancreas, duodenum, and proximal jejunum in 10 patients. Six of these patients had duct cell carcinomas with extensive liver invasion. Although follow-up was still brief at the time of publication (3 to 9 months), five of the six patients with duct cell tumor were alive and free of detectable disease. The early success of these operations for a very unfavorable tumor type remains promising, but the long-term follow-up will be extremely important in determining the efficacy of this radical treatment.

Other Primary Hepatic Tumors

This group includes a large variety of tumors, the majority being epithelioid hemangioendotheliomas, angiosarcomas, and hepatoblastomas. Hemangioendotheliomas are, in general, slow-growing but aggressive tumors with a variable natural history.[17] Angiosarcomas have a much less favorable prognosis. Hepatoblastomas are the most common hepatic tumors in the pediatric population. Histologic type determines long-term survival of patients with hepatoblastoma, and resectability may be increased with preoperative chemotherapy.[18]

In the Cambridge series,[10] five patients underwent transplants for primary angiosarcoma. Four died within the first 2 months and the fifth had a tumor recurrence at 6 months. Their only patient with hemangioendothelioma died at 2 years with recurrence in the liver graft. The Hannover series[11] had two cases of hemangiosarcoma. The first patient died at 5 months secondary to disseminated tumor, and the other was alive without disease at 3 years. They also performed transplants on two patients with hepatoblastoma one of whom died in the early postoperative period, and the other remained alive at 6 years following transplantation. This child was found to have mixed epithelial-mesenchymal lesions with an intermediate prognosis.

Koneru[9] has treated seven patients with epithelioid hemangioendothelioma in the cyclosporine era. One patient died of recurrence at 16 months and the remaining six are reported alive. In an earlier report of the Denver/Pittsburgh series, Iwatsuki et al[2] reported one patient with angiosarcoma who died of residual tumor at 3 months and one patient with sarcoma of unknown origin who was alive without recurrence at 8.66 years. They also described one patient with α_1-antitrypsin deficiency and hepatoblastoma who was alive and free of disease over 7 years after transplantation. In a combined series of 10 centers in North America, 12 children were treated for hepatoblastoma by OLT. Half of these children remained alive 24 to 70 months following transplantation.[19]

Metastatic Disease

The liver is the organ most frequently involved with metastases from other organs. Recent studies have shown that hepatic resections for metastatic colorectal carcinomas can provide long-term survival and cure in certain patients.[20,21] However, resection is not possible if the metastases are not isolated and the tumor is studded throughout the entire organ.

The European centers performed the greatest number of transplants for metastatic disease. Pichlmayer[3] reported the results of seven European centers in which 43 transplants were performed for metastatic disease (30 colorectal). Only six patients (14%) were alive 2 years following transplantation and there were no 5-year survivors. In the Pittsburgh series, seven patients underwent transplants for metastatic disease (five neuroendocrine, one leiomyosarcoma, and one adenocarcinoma of unknown origin). Four of the patients with neuroendocrine tumors underwent resection of the primary lesion at the same time as the OLT. Four patients remained alive, two with recurrent disease.[9] In the Cambridge series, two patients underwent transplantation for disabling symptomatic carcinoid syndrome. One died of chronic rejection at 7 months and the other was alive and symptom-free at 12 months. They also performed transplants on six other patients with metastatic disease from various primary sites.

Only three of the six patients survived longer than 3 months, and these three died of recurrent tumor.[10]

As stated earlier, Starzl et al[6] performed abdominal cluster transplantations for foregut derivative tumors. Two of these were sarcomas from the duodenum and two were carcinoids, one from the stomach and the other from the duodenum. All four had extensive liver involvement. One patient died 9 days after requiring retransplantation and developing systemic candidiasis. The other three were alive at the time of publication with a follow-up of 168 to 258 days.

Considering the collective data reviewed above, there is obvious potential for long-term cure with this form of therapy, and no patient should be categorically rejected for liver transplantation. Certain tumors have a very favorable prognosis following OLT, including incidental HCC, fibrolamellar HCC, epithelioid hemangioendotheliomas, and hepatoblastomas. In patients with multifocal HCC found in cirrhotic livers, OLT is probably the treatment of choice, as opposed to multiple resections that leave behind compromised hepatic parenchyma. Patients who do not fare as well, such as those with large symptomatic HCCs, diffusely infiltrative carcinomas, cholangiocarcinomas, or extrahepatic disease, should not be candidates unless they are placed in an investigational protocol, ideally a multicenter national trial.

Careful patient selection remains crucial for the success of this form of therapy. This includes detailed screening and tumor staging prior to transplantation. In any patient with malignancy, the liver transplantation procedure should be planned as an exploration with a donor liver in hand. If any positive lymph nodes or extrahepatic disease are found at that time, then another candidate should be considered for transplantation, although future studies using adjuvant therapy may allow us to include patients with cancerous lymph nodes that are free of extrahepatic tumor. We need to balance prudent judgment and patient selection with the desire to expand the limits of conventional therapy in searching for new and innovative cures.

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Discussion

WILLIAM S. FLETCHER, MD, Portland, Ore: Olthoff et al have done a service by reporting their results and analyzing data from the first decade of liver transplantation for cancer. In the face of modern regional chemotherapy, I doubt that survival is as poor as they suggest. I was stimulated to look at our own experience in the past 10 years.

In the early 1960s, Drs Daniel Dennis, William Awe, Sarah Donaldson, and I worked out the maximum tolerated dose of various chemotherapeutic agents given via the hepatic artery in dogs and then in humans. We found a surprisingly wide range of tolerance and settled on 1 g/d of fluorouracil for 10 days, or 2 g/d for 5 days with virtually no toxicity except mild peptic symptoms. Doxorubicin hydrochloride can be given at 0.4 mg/kg per day for 5 days in patients with mild liver dysfunction or at half that dose in patients with severe liver dysfunction. Cisplatin, velban, vincristine, and mitomycin C can also be given via the hepatic artery, but dosages of methotrexate that are well tolerated systemically are uniformly lethal when given via the hepatic artery. Most patients were given fluorouracil or doxorubicin intravenously weekly between infusions. In recent years, we have also employed chemoembolization of the hepatic artery and, rarely, radiation therapy for the inferior vena cava syndrome, which causes sudden ascites and anasarca of the lower extremities. Good responses are the rule rather than the exception. One patient with extensive ovarian carcinoma to the liver is completely free of disease (by repeated open biopsy) at 19 years. One patient with hemangioendothelioma is alive and well at 14 years, and another patient with breast cancer is alive at 13 years and beginning to develop distant metastases. Almost all hepatomas and metastatic colon cancers limited to the liver respond for 2, 3, or 4 years. I do think that it is important to use some suppressive systemic therapy along with the infusions and chemoembolizations.

The results of our regional chemotherapy in the same tumor types as reported by Olthoff et al are shown in Table 4.

Clearly, there are two populations of patients here—those who respond to treatment and those who die within 1 to 3 months. Presumably the transplantation patients were the better candidates.

This discussion is not meant to diminish the importance of this article. The question is whether a patient with cancer can tolerate the immunosuppression associated with transplantation. Definitely some of them can and may even benefit from it. The problem is one of selection of patients and further definition of the immunobiology of cancer, a most perplexing subject.

In summary, the judicious but aggressive use of hepatic artery infusion, chemoembolization, and possibly irradiation prior to trans-

Table 4.—Results of Regional Chemotherapy*

Cancer Type	No. of Patients	Survival, mo			
		From Diagnosis		From Infusion	
		Range	Mean	Range	Mean
Hepatomas	16	2-49	11	1-48	8.5
Ampullary carcinoma	3	20-102	69	1-89	31.6
Unknown primary	8	1-131	21.5	0.25-24	7.2
Cholangiocarcinoma	12	3-40	13.6	2-40	12.4
Islet cell	20	2-103	44.2	1-88	19.2†
Pancreatic adenocarcinoma	14	3-15	7.6	0.5-14	4.1
Leiomyosarcoma	6	4-77	33.7	2-21	9.7

*Reported by Fletcher et al.
†11 patients still alive.

plantation would not only provide years of additional useful life, but would help select those patients who are not going to get early distant spread. It may even be possible to extinguish the tumor in the liver prior to transplantation or to render it incapable of growing as a metastasis. We are currently working on such protocols with Dr C. W. Pinson and our own liver transplant team. Obviously, infusion catheters should not be placed surgically, a fact that would complicate, if not preclude, a subsequent transplant. I should like to ask the authors about their patient selection. I should also like to ask if there are plans for a national protocol like the one we use in cooperative cancer study groups and which, I believe will be necessary to define the role of liver transplantation for cancer.

THEODORE X. O'CONNELL, MD, Los Angeles, Calif: Do you think it is fair to compare the survival of patients with HCC who undergo transplantation with that of those who are untreated? Obviously, untreated patients had different type and extent of disease (perhaps metastatic) and associated illnesses, while those patients who undergo liver transplantation are the very best of patients. Also, most of the patients with HCC are not going untreated, but are being treated by multiple means including chemoembolization, regional chemotherapy, etc.

The authors strongly recommend adjuvant chemotherapy and chemoembolization in the patients with HCC, but unfortunately, they offered no data in the paper to support this conclusion. Would the authors want us to embolize the newly transplanted liver? What organ would be chemoembolized in that situation?

Since we know that chemotherapy's ineffectiveness in treating HCC is why there is the great need for regional chemotherapy and transplantation, why do the authors think that adjuvant systemic chemotherapy would afford protection?

ALFRED A. DELORIMIER, MD, San Francisco, Calif: Three children were listed as having hemangioendothelioma. Maybe it is a matter of semantics, but hemangioendothelioma is a benign lesion and the natural course of this tumor is to involute. Could we have a little more detail about those three patients?

DONALD L. MORTON, MD, Los Angeles: Some of the newer concepts of metastases coming from the basic laboratory may rationalize some of these extraordinary surgical procedures for the treatment of diseases that metastasize from the primary site to the liver or other organs.

The "favorite soil" hypothesis of cancer metastases first proposed 100 years ago by a surgeon, Sir Stephen Paget, now has a rational explanation. Paget observed that certain neoplasms seemed to seed to certain organ sites (such as sarcomas to the lung) and grow where the "soil" was favorable. The explanation for single organ metastases from a particular tumor was not understood until recently, when it was found that certain organs have adhesion receptors in their vascular endothelium and produce growth factors that are able to support the adhesion and growth of certain types of metastatic neoplasms. That is, a particular malignancy will need a growth factor from the liver or from the lung, so that if one then removes that organ and replaces it with a new organ and there are no other clones of cells at other body sites, one may, in fact, achieve long-term survival, as we have seen here. The nature of these growth factors and adhesion molecules is being intensively studied. This research begins to explain how a patient with malignancy can be given systemic immunosuppression adequate to prevent the rejection of a foreign tissue transplant, yet not have that patient's own malignancy go out of control. This approach may be successful in situations in which there are clones of metastatic cells that are only able to grow in the one transplanted organ.

Infusion chemotherapy and chemoembolization are very toxic to the intima of the arteries, and I wonder how such preoperative treatment might complicate the vascular anastomosis needed for transplantation.

CLAUDE H. ORGAN, JR, MD, Oakland, Calif: Could you explain the rationale for the retroportal lymphatic excision for foregut malignancies? Is this a group of patients in which total lymphoid irradiation should be considered preoperatively? How do you propose in your unit to stratify the use of donor livers where there is a scarcity of them? If you have multiple recipients in a unit, where would you place this group of malignancies in your priority listing?

JAMES E. GOODNIGHT, JR, MD, Sacramento, Calif: The percentage of long-term survivors in the HCC group is essentially the same as for patients resected by conventional means; so with this very aggressive approach, you have selected out an additional group that will go on to long-term survival. The question is, how to select a favorable group for this approach. In particular, what is the role of cirrhosis, the level of α-fetoprotein, tumor size, and perhaps DNA flow cytometry?

Of those 78% of patients with HCC who died of tumor recurrence, where did that tumor occur? Was it in the liver or elsewhere?

DR BUSUTTIL: The concept of offering liver transplantation to patients with unresectable hepatic malignancy is in principle to offer it to only a select group of patients. In some cases of HCC, one can achieve comparable long-term survival with other modalities such as regional chemotherapy or regional chemoembolization. In many of our patients, such modalities were tried and failed. We did not offer some patients with HCC these types of regional therapy because of coexisting end-stage liver disease that was present in two thirds of the patients. Thus, patients who were selected for liver transplantation were those in whom no other conventional therapy would be suitable.

At a recent conference sponsored by the National Institutes of Health in which the various indications for liver transplantation were further analyzed, it was recommended that a protocol be organized within the next year.

How can systemic therapy be effective in an adjuvant setting if it was ineffective in the treatment of HCC? Systemic chemotherapy with the present therapeutic agents is ineffectual with the best survival of 6 to 9 months. However, the use of systemic chemotherapy as an adjunct to removing the entire tumor with orthotopic transplantation may have a tumorocidal effect on those cells that are disseminated during the liver transplant, and perhaps decrease the high incidence of recurrence that we see. We have a protocol for continuous infusion of 5-fluorouracil and administration of doxorubicin and cisplatin in conjunction with liver transplantation for patients with hepatocellular malignancy. We have studied three patients but the follow-up is too short to make any definitive conclusions.

The Baylor group[22] administered doxorubicin to a group of patients with HCC preoperatively, intraoperatively, and for a short time postoperatively. None of the 15 patients had lymph nodes that tested positive, and with a short follow-up, there has been no evidence of recurrence. These results, which appear promising, may be due to the fact that none of the patients had cancerous lymph nodes, a fact that has been shown by other groups to be an extremely important determinant of recurrence after liver transplantation for HCC.

Children with hemangioendothelioma have a different neoplasm than HCC and have a much different natural history. In both adult and pediatric patients with bilobar tumors, these can be very aggressive, and this was the case in all three of our patients who had severely symptomatic disease. In the one child with hemangioendothelioma, the tumor was so large that it caused respiratory embarrassment requiring intubation due to the tumor mass. Previous attempts at surgery, radiation, and administration of steroids were unsuccessful, and thus the only option was transplantation. The patient underwent liver replacement and is now doing well at approximately 5 years, without evidence of recurrence.

Dr Morton has provided us with some information regarding growth factors that may be hepatic-based and that may favor metastatic dissemination of tumors. I do not have any further information regarding that issue, although we do know that when transplantation is indeed performed for metabolic-hepatic–based defects, the recipient takes on the phenotype of the donor, and these defects are no longer present. It would be obviously speculative to think that this might apply to tumor growth factors. In regard to how regional chemotherapy or regional embolization will alter the technical feasibility of subsequent liver transplantation, I believe that I can simply say that it might make the operation more difficult, but would in no way preclude it. There have been significant technical advances in liver transplantation whereby patients are no longer excluded because of thrombosis of the hepatic artery or the portal vein. If either of these are found, dissection is carried proximally to a suitable site of inflow. If the hepatic artery is thrombosed, the site of inflow would be the celiac axis or the supraceliac aorta, and if the portal vein is thrombosed, an iliac vein graft would be used and direct flow from the superior mesenteric vein to the donor portal vein would be used.

It is very difficult to do an en bloc resection of portal vein lymphatics with OLT. This can be accomplished by a foregut resection. The derivatives of the embryologic foregut include the liver, pancreas, stomach, duodenum, proximal jejunum, and transverse and ascending colon. For those lesions that arise in the portahepatis, a foregut resection is the only way that one can clear this area of lymphatic tissue and obtain adequate margins. To maintain circulation, the patient is placed on venous-venous bypass. The entire organ cluster is replaced, or more recently, only the liver is replaced.

Dr Goodnight, liver transplantation is merely an extension of hepatic resection for these tumors. Conventional hepatic resection is the first modality of treatment for patients who have HCC. However, many of these patients are not suitable for resection including as much as 80% of the liver. Either the entire liver is involved or the remaining hepatic parenchyma is so compromised that the patients would die of liver failure following the resection. I believe that any advances that are made in long-term cure with conventional hepatic resection could be applied to liver transplantation.

In summary, liver transplantation should be considered for patients with unresectable hepatic malignancies in patients who have no evidence of extrahepatic disease. Every case needs to be individualized to obtain the best possible results.

Invited Commentary

Liver transplantation has proven efficacious in the treatment of many disorders, with survival probabilities exceeding 90% in some patients. However, its role in the treatment of malignancies remains controversial. This study by Olthoff et al from UCLA is important because it presents a 6-year experience from one of the busier transplant centers in the United States. As a bonus, it also presents a thorough review of the world literature on the subject. What the authors do not do (perhaps because it remains impossible) is settle the controversy. With the increased success of liver transplantation has come increased demand, but without a concomitant boost in the supply of donor organs. With such perspective, this study should signal the end of liver transplantation for treatment of tumors outside carefully planned protocols. The authors' experience and that of others they review provides enough anecdotal data to warrant a cautious approach. We know, for instance that not all tumors are alike; some recur with disheartening regularity, others almost never. We must also recognize that historically, the surgical treatment of certain malignancies has rarely, if ever, failed from lack of surgical temerity The lessons of experience must combine with an acute awareness of social reponsibility to temper the temptation to engage in the spectacular. The pioneer in all of us can seek solace in the hope that a solution to the shortage of donor organs lies in our future.

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Comprehensive Management of Acute Necrotizing Pancreatitis and Pancreatic Abscess

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• **Achieving reduced mortality rates in patients with necrotizing pancreatitis and pancreatic abscess is possible by employing a comprehensive management plan. Components of the plan include (1) rapid evaluation and assessment of the degree of physiologic and anatomic derangement, the latter by the prompt use of vascular enhanced computed tomographic scan; (2) adequate fluid resuscitation determined by early institution of advanced hemodynamic monitoring; (3) attempts to identify and document septic foci via computed tomography–guided percutaneous aspiration; and (4) aggressive surgical débridement. Close adherence to these policies allowed us to keep mortality in this seriously ill group of patients to 14%. Most deaths occurred in patients who were referred to this service late in the course of their disease. The Acute Physiology and Chronic Health Enquiry (APACHE) II severity of illness index applied at the time of admission proved an accurate predictor of mortality. A score of 25 or greater was highly predictive of death, and a lesser score, of survival.**

(*Arch Surg.* 1990;125:1269-1275)

Trends in the management of acute necrotizing pancreatitis continue to evolve as progress is made in the evaluation and treatment of this disease. Diagnostic workup of patients with severe pancreatitis now routinely involves the use of computed tomographic (CT)[1-4] scanning, usually with contrast enhancement. Furthermore, simultaneous percutaneous aspiration of suspicious fluid collections under CT guidance has made early identification of septic foci possible and thereby allowed surgical drainage to proceed earlier. Improvements in our ability to assess the severity of an episode of acute necrotizing pancreatitis have been developed, initially with the criteria of Ranson et al[5] (and later those of Blamey et al[6] and Corfield et al[7]), and more recently, by application of the Acute Physiology and Chronic Health Enquiry (APACHE) II scoring system.[8] This physiologic-based severity index appears to be a valid method in predicting the outcome of an attack of acute necrotizing pancreatitis. Last, advances in the therapy of this disease, including aggressive fluid resuscitation, hemodynamic monitoring, ventilatory support, and total parenteral nutrition (TPN), augmented by operative strategies such as frequent débridement, peritoneal lavage, and open packing techniques[9] have been proposed and increasingly employed.

The application of these current diagnostic and therapeutic modalities in the management of acute necrotizing pancreatitis have allowed some institutions to achieve survival rates as high as 85%.[9,10] The purpose of this report is to chronicle the senior author's experience with severe acute pancreatitis, and to analyze these results with regard to the severity of illness defined by the initial physiologic derangement.

MATERIALS AND METHODS

There were 50 patients admitted to the Gastrointestinal Surgery Service at the University of California (UC) Davis Medical Center, Sacramento, between 1982 and 1989 requiring operation for complications of acute pancreatitis. All patients presented with either sterile or infected pancreatic and/or peripancreatic necrosis or walled-off infected pancreatic fluid collections that we refer to as *pancreatic abscess*. In truth, a spectrum of the pathologic process was seen involving the combination of necrosis and fluid collection, which at one end of the spectrum was essentially necrosis without fluid, while at the other extreme was fluid without necrosis. We attempted to categorize these patients on the basis of the predominant feature because we believe that there is a difference in prognosis on this basis. Demographic data were collected, including the age and sex of each patient, as well as the origin of the pancreatitis. Days of hospitalization, days of intensive care unit (ICU) treatment, days on mechanical ventilation, and days requiring TPN were recorded.

Extensive radiologic evaluation was undertaken initially and in serial fashion, including ultrasound study and CT scanning. All preoperative CT scans were reviewed by radiologists who were unaware of patient course or outcome, and were graded on a scale of 0 to 4 for both intrapancreatic (IP) and extrapancreatic (EP) findings, listed as follows. For IP, 0 indicates normal; 1, enlargement without necrosis; 2, up to 25% necrosis; 3, 25% to 50% necrosis; and 4, greater than 50% necrosis. For EP, 0 indicates no peripancreatic fluid or inflammation; 1, peripancreatic extension within pericapsular space; 2, inflamma-

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tory extension to a single space beyond the capsule; 3, extension to two or more spaces above the level of the kidneys; and 4, retroperitoneal extension below the level of the kidneys.

Patients admitted to the ICU were aggressively resuscitated with fluids, and had the appropriate level of hemodynamic monitoring instituted as early as possible. Mechanical ventilation was instituted in patients with progressive hypoxemia or tachypnea.

Indications for surgery were the following: (1) documentation of infection by culture or Gram's stain after percutaneous aspiration in pancreatic necrosis or fluid collections; (2) clinical deterioration with strong suspicion of sepsis; and (3) failure to improve after prolonged course of medical management.

Charts were reviewed for these 50 patients and data were collected to allow determination of Ranson score, APACHE II score, fluid balance, and System Outcome Score (SOS). The Ranson, APACHE II, and SOS scores were calculated via previously described methods.[5,8,11]

RESULTS

The etiology of the pancreatitis was alcohol in 17 patients, biliary in 14, endoscopic retrograde cholangiopancreatography (ERCP) in five, trauma in four, hyperlipidemia in four, congenital in two, structural in two, and idiopathic or unknown in four. Two thirds were men, and the average age was 49.5 years with a range of 20 to 88 years.

Thirty-one patients (62%) were initially hospitalized elsewhere and then transferred to UC Davis Medical Center. Onset of symptoms to operation averaged 10 days (range, 1 to 90) for those hospitalized primarily at UC Davis Medical Center and 28 days (range, 1 to 180) for those transferred to UC Davis Medical Center.

There were seven deaths in this group of 50 patients, for a mortality rate of 14% (Table 1). Four of these patients had infected pancreatic necrosis and died after protracted courses of multiorgan system failure and sepsis. The remaining three patients had fulminant pancreatitis, two with sterile, predominantly peripancreatic necrosis and fat sequestra, while the third had infected pancreatic necrosis. These patients died after short hospitalizations from intractable hemodynamic and respiratory failure. Of the 43 surviving patients, 31 had infected pancreatic necrosis, nine had pancreatic abscesses, and three had sterile pancreatic and peripancreatic necrosis.

Complicated clinical courses were the rule in this group of patients. The average length of hospitalization for all patients was 59 days, and approximately half of that time was spent in the ICU. Patients required TPN for an average of 43 days, as well as mechanical ventilation for an average of 23 days.

Radiologic evaluation played an important role in the management of these problems. The average patient underwent 3.3 CT scans during his hospitalization, with some patient requiring as many as 10. Preoperative CT scans from ou institution were available on 33 patients, and the majority o these were performed with the technique of dynamic vascular enhancement. The average IP score was 2.53, while the average EP score was 2.25. The distribution of scores can be seen in Fig 1. Thirty-one of the patients underwent CT-guided percutaneous aspiration of pancreatic necrosis or fluid collection for diagnosis or treatment as part of their management.

The number of operations required per patient during hospitalization ranged from one to 18, with the average being 2.8. Twelve of the 50 patients with extensive infected pancreatic and peripancreatic necrosis were treated surgically with a combination of open packing and continuous catheter irrigation. These patients averaged 7.1 trips to the operating room for surgical procedures and nine of the 12 survived. Of those patients managed by closed drainage methods, 42% required reoperation for complications or persistent sepsis. In addition, the total necrosectomy specimen was quantitated in 24 of these patients, and averaged 227 g, with a range of 30 to 2000 g of total necrosectomy.

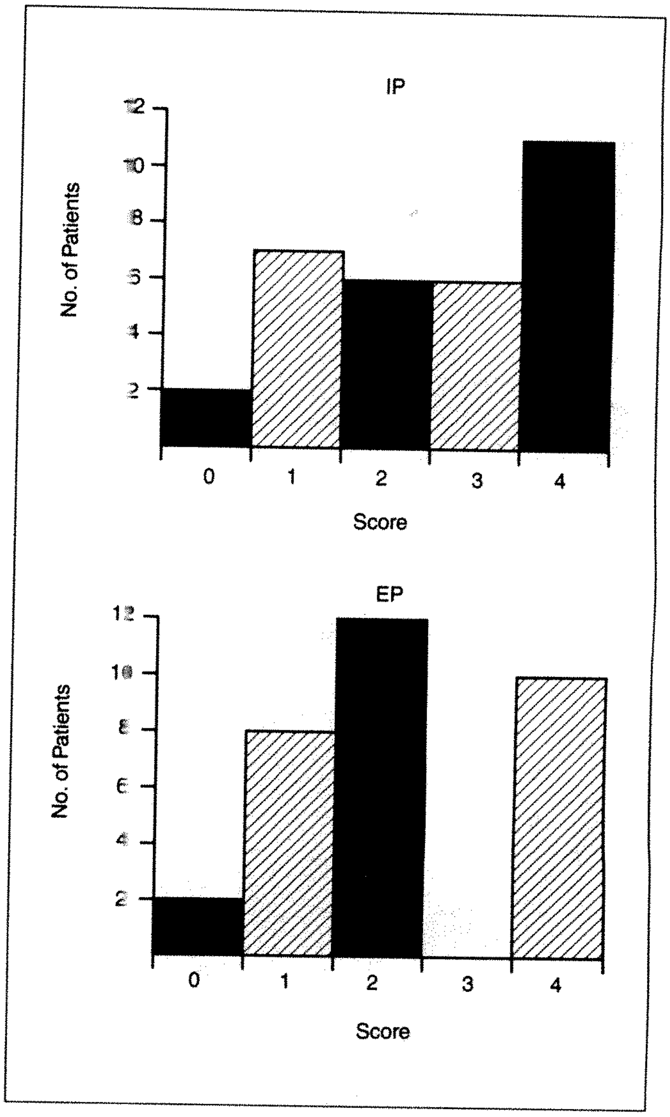
Table 1.—Clinical Data*

Patient	Days From Onset of Symptoms to Admission at UCD	Organ Systems Failing at Admission	Indication for Surgery†	Positive Fluid Balance First 24 h at UCD
A	16	3	1	5
B	1	0	2	4.5
C	25	3	3	9
D	30	4	3	13
E	5	3	3	17
F	9	3	3	10
G	5	2	3	2.5

*UCD indicates University of California, Davis.

†1 represents positive percutaneous aspirate; 2, acute abdomen; 3, clinical deterioration, strong suspicion of sepsis.

Fig 1.—Computed tomographic scores for intrapancreatic (IP) (n = 32; average score, 2.53) and extrapancreatic (EP) (n = 32; average score, 2.26) findings.



The preoperative and postoperative complications are delineated below:

Complications	No. of Patients
Prolonged ileus	41
Adult respiratory distress syndrome	26
Renal failure	15
Cardiac failure or arrhythmia	11
Enteric fistula	10
Pancreatic fistulas	10
Hepatic failure	1

Persistent ileus and the requirement for TPN was the most common complication. Over 80% of patients required TPN, and the patients in this group averaged over 50 days of TPN therapy. Pulmonary, renal, and cardiac failure were the next most common complications noted. Enteric fistulas were encountered in 10 patients. Six patients had colonic fistulas, two had duodenal fistulas, one had a gastric fistula, and one had both colonic and duodenal fistulas. Of the three enteric fistulas in patients treated by open packing, two were present at the initial operative procedure prior to operative manipulation. In contrast, the seven patients treated by closed surgical drainage all developed enteric fistulas after their initial operation. A single patient with an enteric fistula died in this series. Finally, splenectomy was performed in six patients during the hospital course.

Pancreatic fistulas developed in 10 patients, with all cases resulting from external drainage of pancreatic necrosis at the time of surgery. This complication can be expected when the area of necrosis involves the head or midportion of the gland, while a viable, juice-secreting tail remains. The long-term treatment of this problem requires interval ERCP to evaluate the remaining ductal anatomy and abdominal CT scanning following cessation of fistulous output to search for pseudocyst development. In this series, pancreatic fistulas closed in three patients during an average of 11 months, persisted to the present in three patients over an average of 8 months, and were ultimately treated surgically in four patients. In this latter group, three patients underwent internal drainage of pancreatic pseudocysts, while the fourth was operated on for persistent fistula.

As previously mentioned, infection of pancreatic necrosis and fluid collections was frequently seen. Infection was present at the initial operation in 45 patients (90%) of this group and absent in 5 (10%); 22 (50%) were polymicrobial infections. Aerobic gram-negative rods (in 19 cases) and enterococci (in 15 cases) were the most common infecting organisms encountered. The other organisms noted were as follows: *Staphylococcus*, 13; anaerobic, 7; and fungal, 6. The following gram negative rods were found: *Escherichia coli*, 6; *Klebsiella*, 6; *Enterobacter*, 5; *Pseudomonas*, 6; *Serratia*, 2; *Citrobacter*, 2; and *Proteus*, 1.

Survival was examined according to the predominant pathologic process. Nine patients had pancreatic abscess and all survived. Sterile pancreatic and peripancreatic necrosis was seen in five patients, three of whom survived, while infected pancreatic and peripancreatic necrosis was present in 36 patients, 31 (86%) of whom survived.

Analysis of appropriate laboratory and physiologic variables allowed determination of the Ranson, APACHE II, and SOS scores, as well as the initial 24-hour fluid balance. The means and ranges of these values are listed in Table 2. The distribution of APACHE II scores is seen in Fig 2. The average APACHE II score for the entire group was 17.5, with the score for survivors being 14.9, while the score for nonsurvivors was 33.6. The range of scores for survivors was 4 to 27, while for nonsurvivors it was 25 to 43. Of the eight patients with a score greater than or equal to 25, seven died, while all patients with a score less than 25 survived.

Table 2.—Summary of Severity of Illness Variables*

	Deaths	Survivors
APACHE II		
Mean	33.6	14.9
Range	25-43	4-27
Ranson		
Mean	6.8	3.1
Range	2-9	0-10
SOS		
Mean	6.96	1.16
Range	1.75-10	0-6.25
Fluid balance		
Mean	9.7	2.7
Range	4.4-17	0-12

*APACHE indicates Acute Physiology and Chronic Health Enquiry; SOS, System Outcome Score.

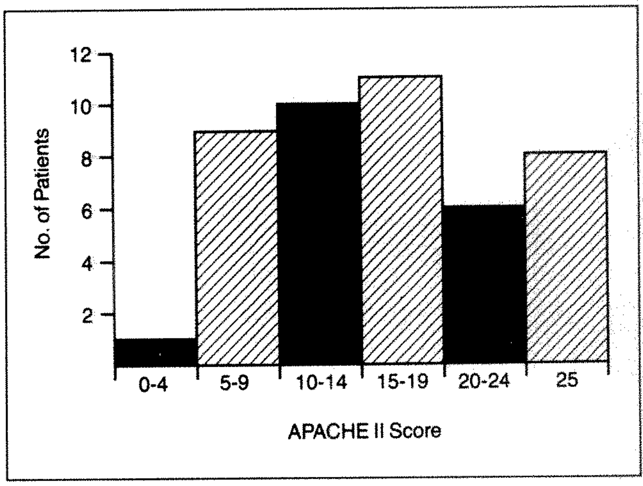


Fig 2.—Acute Physiology and Chronic Health Enquiry (APACHE) II distribution (n = 45; average score, 17.5; range, 4 to 43).

COMMENT

The evaluation and treatment of acute necrotizing pancreatitis continues to be a vexing problem for physicians caring for patients with this disease. The initial pancreatic insult, the release and activation of proteolytic enzymes, the stimulation of systemic mediators of inflammation, and in most cases the addition of bacteriologic invasion combine to form a potentially lethal disease process. Nevertheless, it is possible to achieve high survival rates with this entity by employing a stepwise, multidisciplinary approach that coordinates an ambitious policy of evaluation and supportive care with timely and persistent surgical intervention.

The patients in this series underwent aggressive radiologic evaluation, including multiple CT scans to delineate the extent of the pancreatitis, the presence of necrosis, and the size and location of fluid collections. Previous reports have documented the utility of the dynamic vascular-enhanced CT scan in detecting the presence of pancreatic necrosis,[9,12] and correlations between the extent of glandular necrosis and the risk of subsequent infection have been noted.[13] We have employed this technique in the evaluation of our patients, and found it to accurately parallel the degree of necrosis found at operation. We have also been able to sample these areas of necrosis and fluid collections by percutaneous aspiration at the time of scanning with significant improvement in the ability to objectively identify patients with infection. This has proven to be an invaluable aid in directing the timeliness of surgical therapy. Furthermore, the anatomic assessment of pancreatic and peripancreatic necrosis provided by the CT scan with vascular enhancement appears to be predictive of the development of fistulas, pseudocysts, and endocrine or exocrine insufficiency. Fistulas and pseudocysts can be anticipated when necrosis of the body of the gland is noted in the presence of a viable tail. In this setting, the pancreatic tail continues to secrete pancreatic juice without a conduit to transport it to the duodenum. If contained, this will eventually form a pseudocyst, while if surgically drained externally, a fistula will usually develop.

The principles of supportive care must be rigorously adhered to for these patients to survive. Adequate fluid resuscitation and institution of appropriate hemodynamic monitoring are crucial. We have used predominantly crystalloid solution for resuscitation, and we attempt to maximize cardiac output and oxygen consumption as determined by serial Swan-Ganz measurement, since this has been shown to correlate with improved outcomes.[14] Some patients required as much as 18 L of fluid over the initial 24-hour period to maintain adequate cardiac outputs and filling pressures. In our experience, the amount of time a patient spends in uncorrected hypovolemic shock correlates well with the resultant multiorgan system failure and even death. Six of the seven patients who died in this series presented to our surgical service only after prolonged delays in the recognition of the severity of their illness and in the adequacy of their resuscitation, ranging from 5 to 30 days (Table 1). These patients all manifested terminal multiorgan system failure at admission to our service that failed to respond to medical or surgical management. We are in the process of examining other resuscitative regimens to approach preillness hemodynamic values as early and as closely as possible. The frequency with which adult respiratory distress syndrome was seen in our series also mandates early institution of mechanical ventilation when indicated, as well as the frequently prolonged need for this modality.

The failure of medical therapies to appreciably alter the course of necrotizing pancreatitis has left surgical drainage and débridement as the mainstay of therapy for this disease.[15-20] The treatment of acute necrotizing pancreatitis and its complications, however, is marked by a dichotomy of surgical approaches. Recent reports range from emphasizing aggressive early surgical débridement with ongoing postoperative lavage,[10] to extolling the merits of prolonged supportive care and delay of laparotomy until the development of a chronic mature pseudocyst.[21] The main indications for surgery in this group of patients were previously described. Patients with pancreatic abscess and those with moderate amounts of pancreatic and peripancreatic necrosis were treated by débridement and irrigation, with placement of large silastic catheters for postoperative drainage and occasionally for ongoing lavage. In spite of what was believed to be adequate surgical drainage, over 40% required reoperation for further complications. Figures as high as 66% have been reported in other series.[20]

Patients with massive amounts of pancreatic and peripancreatic necrosis were treated with open packing and continuous postoperative lavage. During the 7 years of this study, our management of patients with acute necrotizing pancreatitis has evolved to include the following indications for open packing: (1) greater than 100-g necrosectomy of pancreatic and peripancreatic tissue at the initial operation; (2) poor delineation of viable from nonviable tissue, with CT evidence of at least 50% pancreatic necrosis; or (3) extensive peripancreatic necrosis involving either the regions anterior, posterior, or superior to the body and tail of the gland, extending below the mesocolon, extending retroperitoneally to the pelvis, or involving the colon or duodenum. Most patients had an IP or EP score of 4. The open packing method with lavage requires frequent repeated operation every 2 to 3 days, but allows constant access to the region of necrosis for débridement of this tissue as well as its proteolytic enzyme content. We were even able to adequately perform dialysis on a patient in complete anuric renal failure with this method. This group of 12 patients averaged over seven trips to the operating room, and 75% of the patients survived.

Enteric and pancreatic fistulas were encountered with moderate regularity in this series, yet did not appear to significantly affect survival. A single patient with enteric fistulas died, while no patient with a pancreatic fistula succumbed. Other investigators have reported mortality rates as high as 25% associated with these entities.[22] Clearly, early recognition and adequate drainage of enteric or pancreatic fistulas is a basic tenet of surgical therapy in necrotizing pancreatitis.

The overall mortality for this select group of patients with severe acute pancreatitis was 14%, with subgroups ranging from 0% in pancreatic abscess to 40% for sterile pancreatic necrosis. Clearly, the presence of necrosis was associated with a higher mortality than abscess (17% vs 0%). The need for operation in the absence of infection also implied a more serious pathophysiologic process and in the two fatal cases, was attributed in part to inadequate fluid resuscitation at the referring hospital.

Similar data from other recently reported series[9,10,23-31] are included in Table 3, demonstrating mortality rates ranging from 9% to 38%, with a cumulative average of 23% for a combined total of 582 patients. The success of our treatment regimen, however, can only be meaningfully interpreted in the context of the severity of illness of the patient cohort. While demographic data regarding the length of patient hospitalization, number of operations per patient, and days spent in the ICU are helpful, the main contribution to prognostic determination in this disease entity was made by Ranson et al in 1975.[5] Their criteria have proved accurate in predicting the severity of an episode of acute pancreatitis, and to a lesser degree, the risk of mortality. The limitations of these criteria, however, are that 48 hours of data collection are required prior to the calculation of prognosis, the degree of physiologic derangement and baseline health status may not be accurately identified, and the ability to identify patients with pancreatic complications may be limited. Indeed, one recent report stressed that only 28% of patients with pancreatic abscesses were identified as having severe pancreatitis by the criteria of Ranson et al.[5]

APACHE II is a classification system developed to correlate the severity of the physiologic derangement on admission to the ICU with the subsequent risk of death during a given hospitalization.[8] This system employs routine physiologic measurements over a 24-hour period in combination with prior health status, and has been validated in almost 6000 ICU admissions from multiple institutions. Advantages of the APACHE II system in acute pancreatitis have recently been detailed, and include the provision of an accurate, reproducible prognostic index that not only allows identification of patients in need of more aggressive forms of monitoring and therapy, but also allows internal quality assurance monitoring and interinstitution comparison of treatment results. The purpose of severity of illness indices are as follows: triage patients, allocation of scarce resources, evaluation of quality of patient care, interhospital comparison, assessment of alternative therapies, and prediction of mortality.

We have applied the APACHE II scoring system to our patients and found the results to be highly predictive. Forty-

Table 3.—Results in Pancreatic Abscess

Source, y	No. of Patients	Severity	Mortality, %
Martin et al,[29] 1984	62	2.1	24
Warshaw and Jin,[30] 1985	45	. . .	24
Crass et al,[31] 1985	21	. . .	19
Pemberton et al,[27] 1986	81	. . .	38
Polk, 1986	27	4.3	33
Fink et al,[23] 1988	100	. . .	20
Beger et al,[13] 1986	74	4.5	8.5
Garcia-Sabrido et al,[24] 1988	49	5.9	27
Larvin and McMahon,[25] 1989	59	. . .	37
Bradley,* 1990	52	5.3	15

*Personal communication.

five of the 50 patients in our series were admitted to the ICU, most at the time of admission, thereby allowing early determination of their APACHE II scores. All patients who died in this series had an APACHE II score greater than 25. Of the 43 patients who survived, only one had a score greater than 25. Therefore, using a score of 25 or greater to predict mortality, all seven deaths would have been accurately predicted and a single survivor would have been inaccurately predicted to die. Similarly, all patients with a score less than 25 would have been accurately predicted to survive. Although attempts were made to use the anatomic score as determined by preoperative CT scanning, to predict severity we have been unable to improve the accuracy of prediction of APACHE II alone.

Further review of the literature demonstrates increasing application of the APACHE II scoring system to intra-abdominal conditions. Levison and Zeigler[32] described 91 patients with intra-abdominal sepsis in whom an overall mortality of 29% was noted. When the APACHE II scores were analyzed, those patients with scores less than 15 were found to have a 1.7% mortality rate, and those with scores greater than 15 were noted to have a 78% mortality rate. In this manner, a more rational analysis comparing percutaneous aspiration with surgical drainage could be performed. Similarly, Bohnen et al[33] prospectively studied 100 patients with intra-abdominal sepsis in whom a mortality of 31% was noted. The overall APACHE II score was 13.72; the average score of those who died was 18.9, while the survivors averaged 11.4. A greater percentage of patients with generalized peritonitis died than of those with localized abscesses; however, the mean APACHE II scores for both survivors and deaths in the former group were greater.

With regard to acute pancreatitis, the APACHE II scoring system has only recently been applied. Garcia-Sabrido et al[24] noted an average APACHE II score of 26.7 for 49 patients with necrotizing pancreatitis, with a mortality rate of 27%. Demmy et al[34] also employed the APACHE II index to their patients with acute pancreatitis and found a 33% mortality rate for patients with a score of 16 to 20. No survivors had a score higher than 20. Last, Larvin and McMahon[25] recently reported their experience with APACHE II in the assessment of acute pancreatitis. They discovered that an APACHE II score greater than 9 at 24 and 48 hours was highly predictive of a severe case of acute pancreatitis and was superior to other severity indexes in this regard. Moreover, the mortality rate was noted to rise from 30% to 100% with an increase in score from 15 to 20. No patient with a score greater than 20 survived.

The number of patients in our series is too small to draw definite conclusions. Nonetheless, we have found the application of the APACHE II scoring system to accurately predict mortality in our patients. Although previous attempts have been made to correlate biochemical or anatomic changes with prognosis, it appears that the pathophysiologic changes reflected in the APACHE II scoring index are more highly predictive of the risk of mortality. The APACHE II system can also be used for quality assurance purposes by allowing careful review of those patients predicted to survive who did not. Last, by applying this system as a uniform index of severity, meaningful evaluation of alternative therapies and comparison of interinstitutional results can be undertaken. Further use of this system as a means of evaluating the quality of patient care, in assessing alternative therapies, and allowing interinstitutional comparison appears warranted.

Application of the APACHE II severity of illness index to this group of patients at the time of admission to the ICU proved highly accurate in prediction of overall mortality. In our study, a score of 25 or greater was highly predictive of death, while a score less than 25 was universally associated with survival.

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Discussion

THOMAS V. BERNE, MD, Los Angeles, Calif: Two questions remain controversial: when to operate and what operation should be done.

According to Bradley, dynamic pancreatography appears to be good at identifying necrosis of the pancreas. However, it does not identify specific patients who have pancreatic bed sepsis. Consequently, we do not do routine dynamic pancreatography. For us, the most helpful study has been fine-needle aspiration of CT-identified peripancreatic fluid.

In a recent report from the Los Angeles County/University of Southern California Medical Center, fine-needle aspiration was determined to be safe and quite reliable. There were no clinically significant complications. When needle aspiration identified organisms by Gram's stain or culture, pancreatic bed infection always existed. When no organisms were found, only 4% of the patients were later found to be infected. Our strategy relies heavily on a positive needle aspiration as an indication for operative drainage. The authors also operated predominantly on infected cases, but 15% were not infected at the time of the first operation. Some patients should be operated on for fulminant pancreatitis in the absence of infection. Additionally, the fine-needle aspiration will occasionally yield false-negative results. Therefore, the patient who continues to deteriorate despite ICU support should go to the operating room for removal of the necrotic tissue, provision of free drainage, and irrigation even if pancreatic bed sepsis is unproven.

Also controversial is what operative procedure to perform. For most cases, we prefer a synchronous anterior celiotomy and posterior (12th rib) drainage of the pancreatic bed instead of open packing. This provides free dependent drainage without the necessity of large sump drains. Packing may be valuable in cases of extensive necrosis or when excessive bleeding is encountered at the first operation, but it dooms the patient to a large open wound and multiple dressing changes.

Under what circumstances do the authors employ the open packing technique? A unique aspect of this report is the application of the APACHE II scoring to this group of patients. This scoring system appears to have important advantages over other prognostic indexes, but we need verification on larger numbers of patients. There are a few difficulties in applying APACHE II scoring to these cases. One is that such scoring has usually been applied to patients on entry to an ICU. When would the authors suggest that the APACHE II scoring be done in patients with serious pancreatitis?

JERROLD K. LONGERGEAM, MD, Loma Linda, Calif: At Loma Linda over the past 20 years, we have operated on 34 patients with acute necrotizing pancreatitis, classified in three groups. The first group of eight patients had wide débridement of necrotic tissue and either closed sump or anterior open drainage. The second group of 16 patients were treated by near total pancreatectomy. The most recent group of 10 patients had extensive debridement and posterior dependent open drainage via the bed of the resected 11th rib. The first group had a high incidence of recurrent sepsis requiring reexploration, further débridement, and redrainage, averaging 1.5 relaparotomies per case, with a mortality rate of 25%.

The second group with near total pancreatectomy had sacrifice of normal pancreatic tissue and a very high incidence of diabetes in surviving patients. The operative mortality rate was 50%.

The last group was treated as recommended by Dr Berne. The necessity for reoperation for débridement and drainage has decreased to an average of 0.5 reoperations per case and the mortality rate has decreased to 10%.

We have come to the conclusion that débridement and posterior dependent open drainage via the bed of the resected 11th rib is the treatment of choice for this serious problem.

M. MICHAEL SHABOT, MD, Los Angeles: With regard to APACHE II scoring, my only caveat would come from Knaus and coworkers,[8] the developers of that standard, who would argue that APACHE-based outcome statistics are best analyzed within specific disease categories. As such, it may not be valid to compare the authors' results for surgical necrotizing pancreatitis with those of previous studies for acute pancreatitis per se. It is more important that they have helped establish new standards for APACHE scoring in necrotizing pancreatitis.

The authors' aggressive approach has yielded no mortality in patients with APACHE II scores less than 25. Only a small minority of patients with scores over 20 are admitted to ICUs, and their mortality rates range from 30% to 80%. As such, the authors have presented new and very high severity-adjusted standards for the treatment of patients with surgical necrotizing pancreatitis.

L. WILLIAM TRAVERSO, MD, Seattle, Wash: In Seattle, we use endoscopic retrograde pancreatography liberally in all patients who are not doing well with their pancreatitis. Endoscopic retrograde cholangiopancreatography combined with endoscopic pancreatic stent and percutaneous placement of a drainage catheter has given us an endoscopic and percutaneous view of these cases of pancreatitis. In the majority of cases there is a pancreatic duct blow-out usually at the genu of the pancreatic duct. This results in a peripancreatic fluid collection. The fluid collection becomes infected and the patient gets peripancreatic necrosis.

The important distinguishing factor in the semantics that we all wrestle with in this disease is that there may be a parenchymal necrosis and then peripancreatic necrosis. Of our last 65 patients, those who have a pancreatic duct blow-out and peripancreatic fluid collection associated with sepsis and peripancreatic necrosis will do well with endoscopic placement, transduodenally, of a pancreatic duct stent combined with a percutaneous drain. These procedures, combined with TPN and somatostatin, allow these patients to close the blow-out and to avoid surgery, especially if their origins are either idiopathic or iatrogenic.

Of patients whose disease has an alcoholic or biliary origin, half can avoid surgery, but the remainder need additional surgical fistula management or débridement.

Have you seen this pancreatic blow-out, and if so, would you consider the more liberal use of pancreatic duct stenting? I would stress that there is no role for percutaneous or endoscopic methods when there is parenchymal necrosis, and drainage of such abscesses through catheters is unwarranted. However, interruption of ongoing peripancreatic necrosis by early use of these new methods may prevent the need for surgical débridement.

RUSSELL A. WILLIAMS, MD, Torrance, Calif: Four years ago, Nordestgaard et al[1] presented a plan for management of pancreatitis using CT scan.

Patients are graded A, B, or C wherein, if the process extends beyond the pancreas on CT, it is a grade C. Grade C patients are treated in the ICU with the expectation that complications will develop in 30% of this group. They receive antibiotics, and are scanned at weekly intervals, if they are not progressing well clinically, to detect signs of infection on the CT.

The finding of a phlegmon on CT scan is not an indication for operation. Operation on a phlegmon is counterproductive and will surely result in infected pancreatitis. There were a number of patients in the authors' study who had operation and then the pancreatic inflammation subsequently became infected.

The physical signs of pancreatitis infection and pancreatitis are so similar that the CT scan with needle aspiration helps to make the distinction. A fluid collection of less than 7 cm in diameter seen on CT scan can be anticipated to resolve, provided there is no infection. Necrotic material alone on CT scan is not an indication for operation, but this is highly likely to become infected especially if an operation is done, leaving drains in place or from the TPN intravenous lines or necrosis of adjacent bowel such as the duodenum or transverse colon.

How accurate are the techniques that the authors use to identify necrosis, particularly the CT scan enhancement? Three of four of their criteria for operating were clinical. Would they ever consider simply basing their need for operation on the results of these enhanced CT studies?

HAILE T. DEBAS, MD, San Francisco, Calif: There is a dichotomy in approach that exists in the management of necrotizing pancreatitis on both sides of the Atlantic Ocean. The French and German surgeons are very aggressive in operating on patients in whom the contrast-enhanced CT scan shows necrosis.

Surgeons on this side of the Atlantic, however, have not so readily accepted that approach. Indeed, the discussions by Drs Berne and Williams suggest that this is the standard that we are now employing. I would like to ask the authors specifically whether severe necrotizing pancreatitis in the absence of sepsis is an indication for surgery.

ROBERT C. LIM, JR, MD, San Francisco: Regarding CT with vascular enhancement, is this done with a single bolus intravenous injection or is it done using selective mesenteric arterial injection along with CT scanning? Were these findings used by the authors in their scoring?

DR FREY: Dr Berne, sepsis and infection are indications for operative intervention. Computed tomographic scan–guided aspiration for Gram's stain and culture is helpful in the early identification of infection.

We do not advocate operating on patients in whom the CT scan with intravenous bolus vascular enhancement shows necrosis. Some patients may never become infected. It is better to wait as long as possible before intervening, that is, 3, 4, or 5 weeks or more, as long as the patient remains uninfected. The delay allows the body to wall off the necrotic process so that the differentiation between viable and nonviable tissue is more apparent at operation. However, those patients with necrosis who deteriorate hemodynamically or develop multiple organ failure should be operated on even if there is no evidence of infection. This group represents a small percentage of those with pancreatic necrosis and the complications occur early in the course of pancreatitis. The mortality is higher the earlier the surgeon has to intervene after the onset of symptoms.

We do not advocate open drainage on all patients. Most of these necrotizing processes have both a solid and a liquid component, the distribution of which varies from patient to patient. We recommend open drainage in patients having a high percentage of necrotic pancreatic and peripancreatic tissue, and when the distribution between viable and nonviable tissue is poorly defined. We débride all necrotic tissue we can find at the initial débridement, but find more necrotic tissue at subsequent débridements. We perform the first three to four open packings in the operating room and subsequent procedures in the ICU at the bedside.

I support Dr Berne's recommendation about adding a flank incision on either side if needed, in addition to our standard bilateral subcostal incision. This is very helpful in getting at the retroperitoneal necrosis, which can extend beneath the colon bilaterally. We do not remove the 12th rib. We make a separate, relatively small 6- to 9-cm incision in the flank that allows us to access the necrotic debris posterior to the pancreas and colon.

Dr Traverso, we have been interested in ERCP in necrotizing pancreatitis. Dr Gebhardt[35] in Nuremburg, West Germany, has reported an extensive experience with ERCP in acute pancreatitis. If there is necrosis of the body of the pancreas, and the tail is viable, there is no place for the pancreatic secretions from the tail to reach the duodenum, and a fistula or pseudocyst results.

I have not had experience with the stent techniques in dealing with peripancreatic fluid collections. I do not know how the stent would help when 300 or 400 g of necrotic tissue has to be débrided.

Dr Williams, the CT scan with bolus intravenous vascular enhancement is very accurate in detecting pancreatic necrosis, but the decision to remove pancreatic tissue is made at the time of operation.

Dr Debas, I do not think there is a great dichotomy at the present time between what is being done in Europe and the United States with regard to operative indications in necrotizing pancreatitis. Dr Beger in Ulm, West Germany, who has led the way in improving our understanding of necrotizing pancreatitis, initially had very liberal operative indications for operating on necrosis, but his operative criteria now are very similar to ours. He operates for infected necrosis, and among patients with uninfected necrosis, only on those who are deteriorating hemodynamically or are developing multiple organ failure.

Surgical Anatomy Question

Q The midgut begins at the pylorus and ends at the midportion of the transverse colon. [True or False?]

A [False] "The midgut extends from halfway along the second part of the duodenum to the left colic flexure."[1]

1. Snell RS. *Clinical Embryology for Medical Students.* Boston, Mass: Little Brown & Co Inc; 1972:136.

Comprehensive Management of Renal Failure in Infants

David Tapper, MD; Sandra Watkins, MD; Mark Burns, MD; Robert O. Hickman, MD; Ellis Avner, MD

• From 1986 through 1989, 23 infants (18 of whom were <30 days old) required peritoneal dialysis within their first 6 months of life. Modifications to conventional peritoneal dialysis included modified Silastic Tenckhoff catheters, peel-away sheaths for percutaneous insertion, automated peritoneal dialysis "cyclers," and generous omentectomy. With these modifications, there were no bowel perforations, and the infants were successfully dialyzed for prolonged periods. Eight of the 23 infants developed end-stage renal failure and were prepared for transplantation. All had gastrostomy tubes placed to supplement oral nutrition. Living, related transplantation was performed when the child weighed 10 kg. Four of the eight completed this protocol. One child with congenital nephrotic syndrome died before transplantation. One transplant was complicated by a technical problem (venous thrombosis), which resulted in allograft loss and return to peritoneal dialysis. Kidney function, growth, and development in the survivors were excellent.

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Successful long-term treatment of the newborn or infant with renal failure requires a comprehensive combined surgical and medical approach. Technologic advances in the treatment of individuals with renal failure have allowed many children to survive who previously would have died. As our expertise has improved in treating younger children, we sought to extend these technologies to younger infants and even to newborns. In the past, newborns and infants who were born with or developed acute renal failure often died because of our inability to dialyze them effectively. In addition, newborns and infants with chronic renal failure were not deemed candidates for long-term dialysis therapy because of their poor long-term outcome in addition to limited technology.

Chronic renal failure in infants is associated with severe neurologic and growth retardation. Rotundo et al[1] retrospectively analyzed 23 patients with renal failure in the 1st year of life who were not dialyzed and found that 87% ultimately developed profound neurologic abnormalities evidenced by developmental delay, hypotonia, seizures, and dyskinesia as well as inadequate statural growth. In a similar report, McGraw and Haka-Ikse[2] studied 12 patients with chronic renal failure from infancy who had undergone early dialysis and transplantation. Eighty percent of these patients subsequently functioned in the subnormal range, and 50% were clearly retarded.[2] It is extremely difficult to achieve catch-up growth in the infant with chronic renal failure despite careful attention to renal osteodystrophy and the use of adequate energy intake. The most severe growth retardation and loss of growth potential occur in infants with chronic renal failure, and most of this growth failure occurs in the first few months of life.[3]

Recognizing the disabling effects of chronic renal failure on the growing infant, we sought to develop an approach that would allow us to treat neonates with chronic renal failure better. We used techniques to dialyze the smallest infants aggressively, maximize their nutrition, and correct metabolic abnormalities, thereby enabling them to survive and grow, followed by early transplantation. Our long-term goal was to avoid the severe neurologic and growth retardation characteristically seen in children with chronic renal failure.

PATIENTS AND METHODS

Patient Population

During the 3-year period between July 1986 and July 1989, twenty-three infants required institution of dialysis within their first 6 months of life. Of these, 18 required dialysis within the first 30 days of life. The cause of the renal failure was most often secondary to hypoxia/hypotension associated with birth asphyxia or to corrective cardiac surgery for a potentially lethal congenital heart defect. These children had oliguria/anuria and were severely acidotic. They frequently experienced fluid overload and required the institution of dialysis to normalize their fluid balance and correct their electrolyte abnormalities. Five children began undergoing dialysis between 2 and 6 months of age. The cause of the chronic renal failure in these children was severe bilateral renal dysplasia in two, congenital oxalosis with multisystem oxalate deposits and severe oxalouria in one, renal failure after an arterial switch procedure for transposition of the great vessels in one, and severe nephrotic syndrome with marked proteinuria and acidosis in one. This last child began dialysis at 6 months of age subsequent to bilateral nephrectomies.

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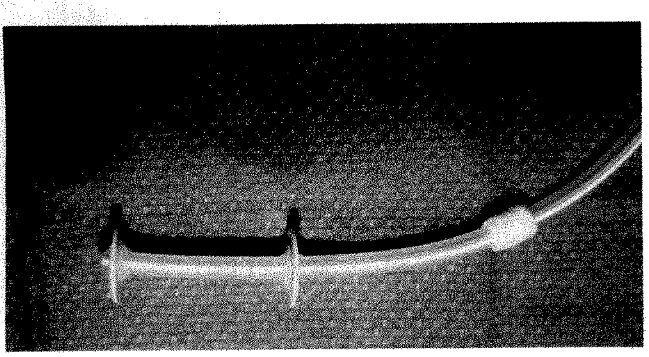

Fig 1.—Double-disk Oreopoulos catheter made of Silastic with multiple holes between the disks. The disks tend to keep the intestine from occluding the catheter.

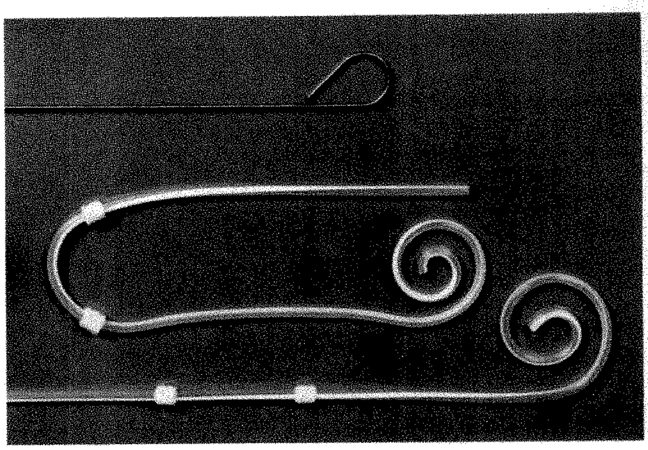

Fig 2.—Curled catheter can be placed percutaneously via a trocar. After placement, the catheter curls under the abdominal wall and is designed to prevent the intestine from wrapping around the catheter and occluding the holes.

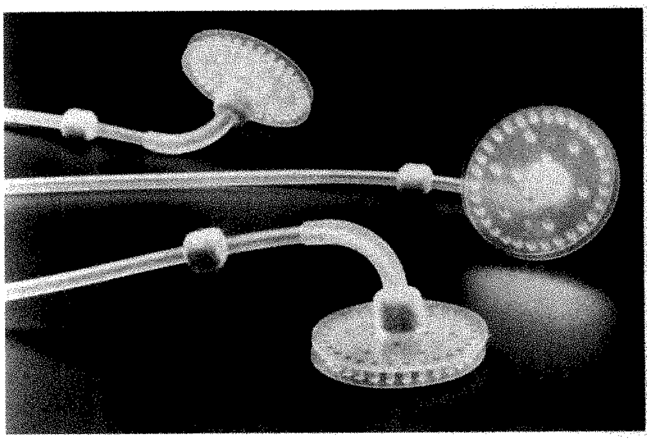

Fig 3.—Showerhead catheter is placed directly beneath the anterior abdominal wall; its showerhead design is constructed to prevent occlusion by intestine or omentum.

Technical Modifications

The institution of successful peritoneal dialysis required modifications in the catheters used as well as the dialysis machinery.

Peritoneal Catheters.—The initial approach was to use a percutaneously placed peritoneal catheter. First, a 5-F feeding tube was passed into the bladder to ensure bladder decompression. A small midline incision was made through the subcutaneous tissue, which had been infiltrated with 0.5% lidocaine. An 18-gauge needle was inserted, and the abdominal cavity was filled with 150 mL of saline. With the Seldinger technique, a guide wire was placed, followed by a dilator with a peel-away sheath. A modified 10-F infant Tenkhoff catheter (Davol Inc, Cranston, RI) was then inserted and the sheath removed. The catheter was sutured in place and dialysis begun. An 11-F introducer and peel-away sheath was used in some children. Presuming the need for long-term peritoneal dialysis, we tunneled the catheter beneath the skin to leave the cuff in the subcutaneous tissue. Not infrequently, these catheters stopped functioning and required replacement. In those children in whom renal failure was resolving and who required only a limited course of dialysis, these catheters were removed over a guide wire and replaced by means of the previously placed tract. The most frequent cause of malfunction was omental occlusion of the catheter's multiple holes. Children requiring long-term peritoneal dialysis underwent operative placement of the catheter and omentectomy.

The modified infant Tenkhoff catheter was the initial catheter most frequently used by our group. Several modified catheters were developed for infants whose catheters repeatedly occluded. We found the double-disk Oreopoulos catheter (Accurate Surgical Instruments, Toronto, Ontario) to be useful (Fig 1). At operation, a small incision was made below the umbilicus, in the midline, and the catheter was placed. The two disks are designed to keep the small intestine away from the catheter to prevent obstruction of the multiple orifices in the catheter. The catheter was tunneled below the rectus muscle, exiting on the lateral abdominal wall. The Dacron cuff was placed beneath the rectus muscle extraperitoneally. We also used straight catheters, pigtail catheters, and showerhead catheters (Quinton Instrument Co, Seattle, Wash) (Figs 2 and 3).

Omentectomy.—Children with chronic renal failure who required operative placement of a peritoneal dialysis catheter underwent a generous omentectomy at the time of catheter replacement. The omentum in these neonates and infants is thin and flimsy. Despite its size, it can effectively occlude all types of catheters that are placed. We removed as much omentum as possible through the midline incision before placement of the catheter.

Gastrostomy Tube.—Nutrition is extremely important in these tiny infants with chronic renal failure. To provide continuous access to the gastrointestinal tract, both for nutrients and for oral medication, we placed a standard Stamm gastrostomy tube through a small left rectus muscle splitting incision at the time of insertion of the peritoneal dialysis catheter. A No. 16 Malecot gastrostomy tube was placed into the stomach and secured with two purse-string sutures. The anterior wall of the stomach was sutured to the anterior abdominal wall, and the catheter was brought out through the incision. There was generally no contamination of the peritoneal cavity when the tube was placed. Postoperative peritoneal dialysis was modified by using smaller inflow volumes for 4 days postoperatively to allow for sealing around the catheter. At 2 months the Malecot tube was changed, in an office procedure, to a No. 18 Silastic gastrostomy button.

Automated Peritoneal Dialysis Cycler.—After placement of the peritoneal catheter, the infants were immediately dialyzed by means of a manual method of instilling fluid and draining the peritoneal cavity. Inflow volumes began at 20 mL/kg and were gradually increased to 50 mL/kg as tolerated. Standard peritoneal dialysis solution (Baxter-Travenol PD, Baxter-Travenol Co, Chicago, Ill) was used, with potassium being added as needed. In most cases 100 U/L of heparin was also added to the dialysate. Dwell times (varying from 10 minutes to 2 hours) and dextrose concentrations (1.5% to 4.25%) were adjusted to provide optimal solute clearance and fluid balance.

When long-term dialysis became necessary, the infants were dialyzed with a cycler (Baxter-Travenol Pac-X, Baxter-Travenol Co). This automated cycler allows the sterile delivery of multiple infusions during the night while the infant sleeps. Inflow volumes, dwell times, drain times, and total number of cycles are preset at the initiation of dialysis. Beginning in 1988, we trained the parents and support personnel to operate the cycler and perform dialysis at home. Infants could then be allowed to experience their normal home environment while receiving dialysis at night as they and their parents slept.

Renal Transplantation.—Eight of the 23 infants had irreversible end-stage renal disease and were prepared for transplantation. Liv-

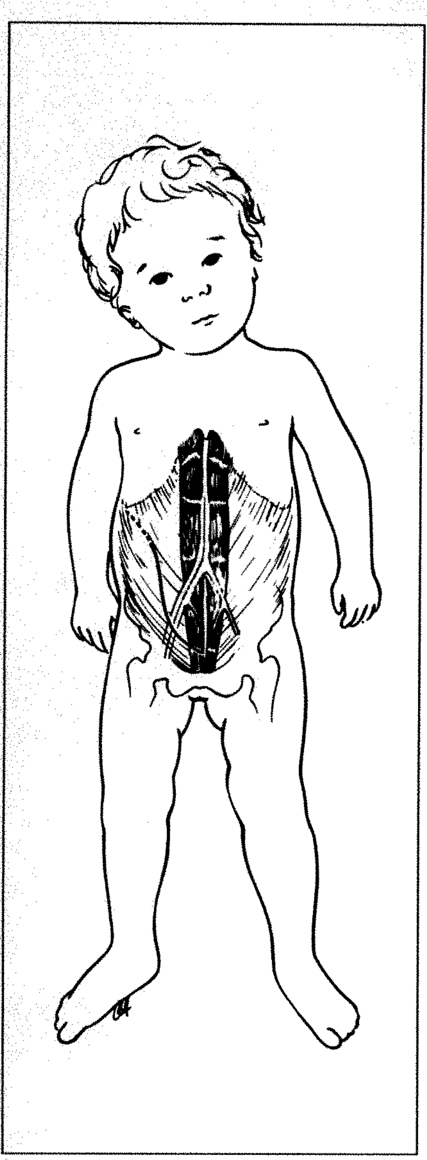

Fig 4.—A hockey-stick incision is made beginning at the midline and curving up toward the costal margin. The rectus muscle is transected and the peritoneum is swept medially to expose the distal aorta and its branches and the inferior vena cava and its branches.

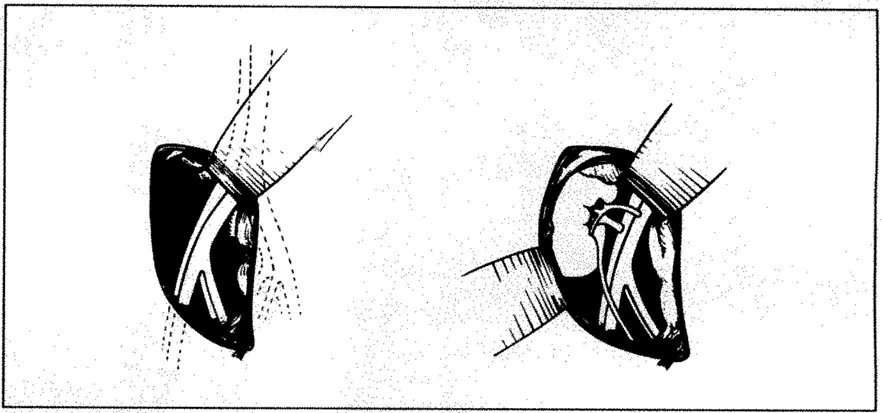

Fig 5.—An end-side venous anastomosis is performed into the recipient's common iliac vein or inferior vena cava. The renal artery is anastomosed to the common iliac artery in an end-side fashion with the use of interrupted horizontal mattress sutures.

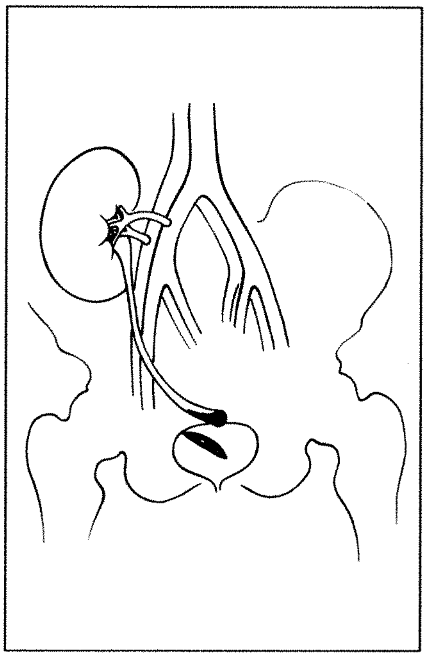

Fig 6.—An extravesical mucosal-mucosal anastomosis of the ureter to the bladder completes the transplant operation. The ureteral-vesical anastomosis is nonrefluxing.

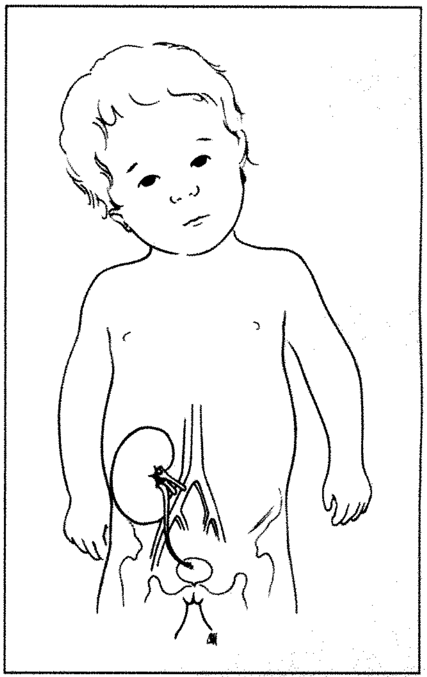

Fig 7.—Completed repair with a large adult kidney fitting snugly in the right iliac fossa in an extraperitoneal position.

ing, related renal transplantation was performed as soon as the child weighed 10 kg (approximately 18 months of age). The approach was extraperitoneal through a generous hockey-stick incision that transected the rectus muscle (Fig 4). We generally prefer to use the right side of the abdomen because it allows better exposure to the inferior vena cava. The vascular anastomoses were performed in an end-to-side fashion to the common iliac vessels or to the inferior vena cava (Fig 5). We used 5-0 polypropylene as a continuous suture for the venous anastomosis and 6 or 7-0 polypropylene for the arterial anastomosis. The sutures for the arterial anastomosis were placed in an interrupted horizontal mattress fashion. The appropriate site on the vessel was chosen before the venotomy or arteriotomy by placing the cooled kidney in the flank and determining the most natural position for the kidney. The venous anastomosis was performed first. All ureteral anastomoses were nonrefluxing. We generally used an unstented extravesical approach either of the Barry type or the Lich Gregoir (Fig 6).[4] Both of these approaches are extravesical and have a mucosal-to-mucosal ureteral-bladder anastomosis and a submucosal tunnel to prevent reflux (Fig 7). The bladder was drained with an appropriately sized urethral catheter.

RESULTS

Peritoneal dialysis was successful all 23 infants. None of the infants suffered any bowel or intestinal complications as a result of the percutaneous placement of the catheter. In 15 of the 23 infants, the renal failure was acute and resolved within 2 weeks of the institution of dialysis. Five of these infants had more than one catheter placed, but none required general anesthesia for the placement of the catheter, and none of these children had either an omentectomy or gastrostomy tube placed.

Eight of the 23 infants had, or developed, end-stage renal disease. All eventually required operative placement of a peritoneal dialysis catheter, and all had an omentectomy and a gastrostomy tube placed. Only one of these children required replacement of the peritoneal catheter due to malfunction during this 3-year period. The routine use of a generous omentectomy combined with a variety of catheter modifications significantly decreased the incidence of catheter malfunction. We extended these modifications to our older patients. Several children developed peritonitis (defined as a white blood cell count of >500 white blood cells per milliliter of fluid or >200 polymorphonuclear cells per milliliter) while undergoing home peritoneal dialysis. The infection rate for peritoneal dialysis in these children was one episode per 12.2 months. After initiation of home cycler therapy, our infection rate dropped to one episode per 15.6 months. All were treated with the instillation of appropriate antibiotics into the dialysate solution, and all but one infection resolved.

Four of the eight children underwent living, related renal transplantation. The youngest patient to undergo transplantation was 10 months old; this patient was diagnosed as having oxalosis and weighed 8 kg at the time of transplantation. The other three were 18 months of age and weighed almost 10 kg. One child is currently undergoing evaluation for living, related transplantation. Two children have no living, related donors and have been placed on the cadaver transplant list. One child died before transplantation. She had congenital nephrotic syndrome with massive ascites secondary to her profound hypoproteinemia. Despite total parenteral nutrition and vigorous enteral nutrition through her gastrostomy tube, we were unable to raise her serum albumin level above 3 g/L. Bilateral nephrectomy was performed in an attempt to diminish her proteinuria, and she began peritoneal dialysis. She developed fungal peritonitis as a result of an intraperitoneal leakage from around her gastrostomy site. This was complicated by massive venous thrombosis, and the patient died.

There was one technical complication in the child whose renal failure was secondary to inadvertent ligation of his distal thoracic aorta at the time of cardiac surgery to close his patent ductus arteriosus. This child had been undergoing peritoneal dialysis for 14 months and weighed 10 kg at the time of surgery. The child received a large kidney from his father. The vascular anastomoses were performed in the standard fashion with the use of the common iliac vein and artery. The child became hypotensive when the vascular clamps were removed despite maximal fluid replacement. Despite adequate flow in the renal artery and vein, as shown by an electromagnetic flow probe, the kidney remained soft and did not make urine intraoperatively. An initial postoperative renal scan showed perfusion but delayed uptake in the kidney and no excretion. A subsequent renal scan, 8 hours later, showed no flow, and the patient was returned to the operating room. Both the renal artery and vein anastomoses were widely patent, but there was extensive thrombus in the renal vein. The kidney was reanastomosed to the distal aorta and the inferior vena cava and the renal capsule was incised. The kidney, however, never functioned and had to be removed. The presumed cause was renal vein thrombosis. The patient returned to peritoneal dialysis and is on the cadaver allograft list.

The three other living, related allografts functioned promptly, with rapid normalization of the serum urea nitrogen and creatinine levels. The child with oxalosis subsequently died of other causes. The two remaining children did extremely well. Both had their peritoneal catheters removed 1 month postoperatively. We continued to use their gastrostomy tubes for supplemental nutrition and as a route for medication. One year after transplantation, the gastrostomy tubes were removed. One child required surgical closure of a persistently draining gastrostomy site, and in the other the gastrostomy site closed spontaneously. Both of these children are functioning normally, growing, and achieving near-normal growth and developmental milestones.

The immunosuppressive regimen in both children included three drugs (prednisone, azathioprine, and cyclosporine) immediately after transplantation, and to date there have been no rejection episodes. Predisone was begun at 3.0 mg/kg and rapidly tapered. By 6 months they were both receiving 0.25 mg/kg and have continued to receive this dose. Azathioprine was started at 3.0 mg/kg and has been decreased to 2.0 mg/kg. Cyclosporine was started at 15 mg/kg and tapered on the basis of trough cyclosporine levels. At 6 months the patients were receiving 4.0 mg/kg, with a whole-blood cyclosporine level ranging between 50 and 100 mg/dL. We have tried to keep the cyclosporine level below 100 mg/dL. Both children function well in preschool environments.

COMMENT

The comprehensive treatment of renal failure is a more hazardous undertaking in children than in adults. This is particularly true when one is faced with a neonate or infant with renal failure. Whereas the techniques for dialysis and transplantation have become more standardized in the adult and even in the child, the neonate presents unique challenges that require a variety of modifications in the dialysis therapy and renal transplantation. In this study we showed that, through adaptation of dialysis catheters and improvements in mechanized dialysis cycling, even the smallest neonate can be dialyzed safely. The primary indication for renal transplantation in the infant and young child is the prevention of growth retardation and the achievement of normal neurologic development. Although our numbers are small, the success of functioning transplanted kidneys and the normalization of growth and neurologic development in our group prompts us to continue with this approach.

Eighteen neonates began undergoing peritoneal dialysis within the first 30 days of life. Fifteen of these neonates were treated with peritoneal dialysis until their renal function returned. None of these children showed any untoward effect of early dialysis. The management of their electrolyte abnormalities and fluid overload was simplified by the judicious use of peritoneal dialysis to correct their electrolyte levels and remove excess fluid. There were no intestinal complications related to the percutaneous placement of the peritoneal catheter, and no patient developed peritonitis.

The infant with chronic renal failure is significantly more affected. Unlike the child, who shows a linear progression from mild to moderate to chronic renal failure, these infants generally have either bilateral congenital dysplasia or have suffered a catastrophic event that has significantly interrupted the blood flow to the kidneys and led to cortical necrosis.[5] The challenge in these infants is to maintain fluid, electrolyte, and mineral homeostasis, correct the uremia, prevent renal osteodystrophy, provide adequate energy intake to achieve growth, and develop techniques for successful transplantation in these infants. These infants were previously thought to be at highest risk for permanent developmental and statural retardation as the result of uremia occurring during a critical developmental stage.[6,7] This study, as well as others, has shown that successful transplantation can obviate the previously predicted poor outcome.[8-11]

The overall plan for the child with renal failure must weigh the potential benefits of early transplantation against the benefits of delayed transplantation and prolonged dialysis. Factors involved in this determination include the safety of the operative procedure and the risks of administering immunosuppressive drugs, the chance of obtaining a successful result, and the reversibility of neurologic and skeletal damage that may have been sustained by the developing child in the pretransplant uremic environment. Individuals who develop chronic renal failure as children usually do not achieve an adult height consistent with their genetic potential.[6] Although some of these individuals may attain a final height within the normal range for the population at large, their height is usually subnormal when compared with heights of individuals with a similar genetic makeup.[12]

The important variable affecting growth appears to be the age at onset of chronic renal failure; the poorest growth and the greatest loss of growth potential occur in infants with chronic renal failure, and most of this growth failure occurs in the first few months of life.[12] Unfortunately, the stunted growth of these infants, and many older children with chronic renal failure, is often present at the time of diagnosis. Although appropriate treatment of these children during midchildhood and predialysis years is associated with steady and fairly normal growth, catch-up growth is rarely observed. In recent years there has been improvement in the mean growth velocity of children undergoing long-term hemodialysis therapy, but the height SD scores of these children remain significantly below normal.[13] Children treated with long-term peritoneal dialysis also exhibited subnormal height SD scores in most but not all studies.[6] Although it may not be surprising that children undergoing dialysis rarely exhibit catch-up growth, it has been shown that catch-up growth was rarely observed in children who received a renal transplant.[2] Our findings disagree with this contention. We, like others, have shown that catch-up growth is possible after renal transplantation if (1) the patients underwent transplantation at an early age, (2) they were given a low daily maintenance prednisone dose (<0.25 mg/kg), and (3) they had a normal creatine clearance (>1.50 mL/s per 1.73 m^2).[8-10]

To attempt early transplantation in the infant, the neonate must be successfully dialyzed and provided with an appropriate amount of energy intake to grow. We have found that a generous omentectomy at the time of placement of a long-term peritoneal dialysis catheter has decreased the need for frequent replacement of a nonfunctioning catheter. The placement of a gastrostomy tube has afforded us reliable access to the gastrointestinal tract and allowed us to provide appropriate energy intake. Complete nutritional supplementation can be provided with readily available formulas, which can be drip fed at night if necessary. Excess fluid can be removed by increasing the concentration of the dialysate. The automated peritoneal dialysis cycler has allowed us to teach parents to perform home peritoneal dialysis.

Certain modifications in the transplant operation need to be made so that the infant can accept an adult kidney. We have found that appropriate exposure of the recipient vessels can be achieved through a generous hockey-stick incision by transecting the rectus musculature. One of our patients (who weighed 10 kg) received a kidney from his father, who weighed 125 kg. This fit snugly in the right iliac fossa and right flank, and the vascular anastomoses could be performed without difficulty. We have used the common iliac vein or the inferior vena cava, depending on the size of the donor vein and the recipient vessel for the venous anastomosis. For the arterial anastomosis, the common iliac artery is satisfactory, obviating the need to cross-clamp the distal aorta. We believe that an interrupted arterial anastomosis with the use of horizontal mattress sutures provides for the best approximation and allows for subsequent growth. None of the recipients had been heparinized. It is important for the anesthesiologist to raise the recipient's intravascular volume significantly. We have tended to increase the central pressure to greater than 14 mm Hg so as to prevent hypotension when the vascular clamps are removed. The ureteral anastomosis should be nonrefluxing. We use the unstented extravesical approach, as this diminishes the amount of bladder bleeding and clot formation. Clots can easily occlude the small urethral catheters required to drain the bladder, and the extravesical approach minimizes hematuria. All patients undergo postoperative renal scanning and renal ultrasound. The increment between the appearance of isotope in the distal aorta and the kidney can be used as an indicator of renal perfusion. Subsequent scanning and ultrasound are performed as necessary to guide rejection therapy.

We believe that a living, related transplant in these infants has contributed to the success in achieving normal growth rates. The incidence of rejection episodes with a living, related transplant is less, and therefore the total amount of steroids used is also significantly lower. The use of cyclosporine as part of the immunosuppression regimen has also been important. Knight et al[10] showed that catch-up growth is more prevalent in children treated with cyclosporine alone as opposed to those treated with prednisone and azathioprine. Whether this phenomenon is related to the steroid-sparing effect of cyclosporine or another mechanism remains to be determined. We believe that the multimodal immunosuppression regimen has sharply decreased the number of rejection episodes and that the infants are more likely to have a more normal creatine clearance, which is important for growth. In addition, multimodal therapy allows for more rapid tapering of the prednisone.

The infant with congenital nephrotic syndrome presents an intriguing dilemma. These children characteristically have profound proteinuria with normal serum creatinine levels and poor growth. We urge pediatric nephrologists to consider transplantation earlier in these children. Catch-up growth is difficult to achieve in the child with severe proteinuria of long duration. A successful living, related transplant will afford a better opportunity to achieve near-normal growth. Our patient with congenital nephrotic syndrome died of overwhelming peritonitis before transplantation. We were never able to maintain a normal serum albumin level, and she had massive ascites. In retrospect, an earlier nephrectomy might have prevented her severe wasting and allowed growth to an acceptable weight for transplantation.

The recent availability of recombinant human growth hormone may be an additional tool to help achieve normal growth. Recent trials have shown that children with chronic renal failure receiving 0.125 mg of growth hormone subcutaneously three times a week for 9 months have experienced full catch-up growth.[14] Their growth velocity was above normal during the 9-month observation period.[14] No evidence of anti-human growth hormone antibody development or insulin resistance was detected. The use of recombinant human growth hormone during dialysis and after transplantation needs to be studied.

We believe that the prognosis for children affected with renal insufficiency since infancy, a substantial portion of the population of children with renal failure,[3] is not unusually bleak. Such patients have the potential for normal growth. Renal transplantation is an option that should be presented to parents with affected children as a reasonable treatment with the possibility of an acceptable result.

We wish to thank the Quinton Instrument Co for providing photographs for publication in this article, as well as Betty Krueger for her expert assistance in preparing the manuscript.

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Discussion

ALFRED A. DELORIMIER, MD, San Francisco, Calif: My comments reflect the experience of Dr Oscar Salvatierra with more than 40 renal transplants when renal failure developed in infants younger than 6 months. Infants and children undergoing dialysis do not grow; they have significant mental retardation, and peritoneal dialysis is the only practical method of controlling uremia. Most children undergoing peritoneal dialysis for more than 2 years die. Currently, our nephrologists use nasogastric tube feedings, where a variety of formulas have been tried, but P.M. 60/40 has seemed to work the best.

Infants are also prone to develop recurring peritonitis associated with peritoneal dialysis. Can the authors tell us if the episodes of peritonitis they encountered actually involved the eight patients undergoing long-term dialysis, and therefore the incidence approached 40%? In my experience there is at least one episode every 6 months in the infant age group, and 100% of the infants had at least one episode by 1 year of age. Recurrent peritonitis is a significant morbid problem, which not only contributes to the nutritional deficit but produces progressive adhesions and diminished absorbing surface of the peritoneum, causes intestinal obstruction, and becomes a significant technical problem at the time of renal transplantation to gain access to the retroperitoneum. Further, the immunosuppressive treatment after transplantation may result in septic complications from residual peritoneal contamination.

Our transplantation team strives to proceed with renal transplantation as soon as plateauing in length occurs or when peritonitis develops. In the very small infants, a living, related donor becomes a problem of providing sufficient room, and our transplant service strives to provide a cadaver kidney from a child.

When peritonitis cannot be controlled, the peritoneal catheter has to be removed and a double-lumen atrial catheter is required for hemodialysis until the peritonitis resolves. This requires 1 U of blood to prime the hemodialysis machine each time that dialysis is carried out, and this exposure to the many blood donors will adversely affect the survival of the cadaver transplants. The graft survival for cadaver renal transplants in infants in the University of California, San Francisco, experience is better than 80% over a 2-year period. After transplantation, there is a striking change in the growth, well-being, and development and a reduction in hospitalization for these patients. How do the authors maintain a low rate of peritonitis in the infants, and do they plan to use children's smaller cadaver kidneys when they have problems in achieving a weight gain to the 10-kg total?

MARSHALL Z. SCHWARTZ, MD, Sacramento, Calif: This series represents a large experience. Dialysis in infants presents several metabolic, nutritional, and technical problems. Nutritional supplementation is required in these infants; otherwise they will not grow. We have had good results with night feedings using a small feeding tube passed by the parents nasogastrically in contrast to a gastrostomy tube.

The main technical problem that is encountered is leakage around the catheter. Infants under 6 months of age have a very thick abdominal wall, which significantly increases the risk of leakage around the catheter. In the acute dialysis phase, cutaneous placement of the peritoneal dialysis catheter can work sufficiently even though there is a leak around it. For long-term dialysis, particularly at home, this is not satisfactory. For long-term dialysis we have placed the catheters in the operating room through a very small incision. We use a small coiled catheter designed by me and by the Quinton Co. I have not routinely performed an omentectomy because it requires a larger incision, which increases the chances for leakage. I have not found the omentum to cause obstruction of the catheter in small children. I have chosen not to use some of the other catheters that the authors showed, such as the disk or showerhead, because they require a larger incision to place. This increases the chance of leakage and also requires a more major procedure to remove them or to replace them.

I certainly support the suggestion to employ early transplantation. I have also found during the past 12 years that the retroperitoneal approach is the optimum choice for transplanting a large kidney in a small child.

THOMAS V. BERNE, MD, Los Angeles, Calif: At the present time, in many distribution systems for kidneys, there is consideration for giving pediatric kidneys to pediatric patients, but beyond that, there is no special consideration for the problems of retarded growth in children who remain undergoing dialysis. This has been recently recognized by the United Network for Organ Sharing, which is a national organ distribution network. Consequently, Dr Robert Ettinger at UCLA is chairman of a United Network for Organ Sharing committee that is trying to put together a scheme by which children will be given preference in receiving cadaver kidneys, so that the delays for children will not be so great and their mental and growth retardation will be minimized.

ERIC W. FONKALSRUD, MD, Los Angeles, Calif: Is it more important in the older patient than in the infant to keep the catheter in the pelvis between the bladder and the rectum? In older children, if the catheter is not dependent in its position, it does not seem to work well consistently. When the tip is in the flank or upper part of the abdomen, drainage is often suboptimal.

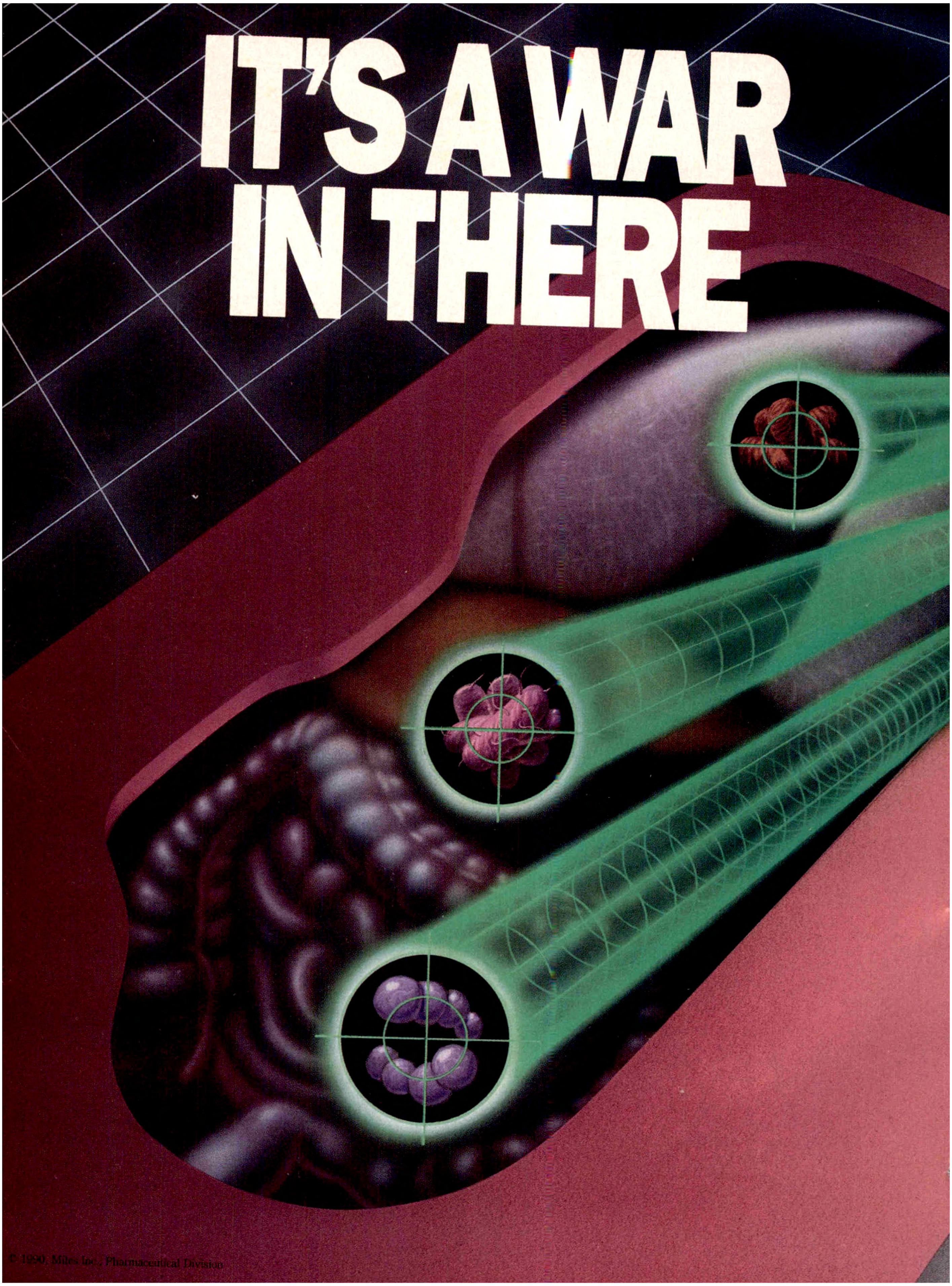
DR TAPPER: I agree with Dr deLorimier that the incidence of peritonitis is higher in patients with end-stage renal disease than in patients with acute renal failure. We evaluated all the children we treated and noted that the biggest improvement followed our switch to the automated cycler; our incidence of peritonitis was one per 12.2 months, but when we went to the cycler, it decreased to one per 15.6 months. The smaller children who undergo long-term dialysis do have a higher incidence of peritonitis.

The use of cadaver kidneys is a difficult issue. The results at the pediatric centers that have done transplantation for long periods have never been able to equal the outstanding results of Dr Salvatierra and his colleagues at University of California, San Francisco. In fact, with cadaver kidneys, kidney function in most of the pediatric centers was only about 30%. There were many rejection episodes, so that the children received such a high cumulative dose of steroids that they did not grow. We felt that if the indication for transplantation were growth, we would drop the age at which we were going to perform transplantation and use primarily a living, related graft.

Dr Schwartz, the modification of the curl or pigtail catheter was the same modification that we applied to the Tenkhoff catheter.

Dr Berne, we are trying to get a variance through the United Network for Organ Sharing so that children on the cadaver lists will be screened first. The results with pediatric cadaver kidneys have been poor, and most transplant centers now refuse to accept kidneys from anyone less than 6 years of age. In the original study the cutoff was 2 years. In pediatric centers they are accepting donors younger than 6 years, and their results, despite combined immunosuppression, are not much better. The proposed United Network for Organ Sharing variance would allow children to be run through the United Network for Organ Sharing list once so that a small child may be matched first.

Dr Fonkalsrud, catheters work better if they are in the pelvis. The problem with young children until the modifications in the catheter was that it would curl and end up on top of the liver, and the dialysis rate was poor. One of the advantages of the curled catheter, the showerhead, and these other modified catheters is that they are shorter. They tend to stay below the umbilicus and in the pelvis.



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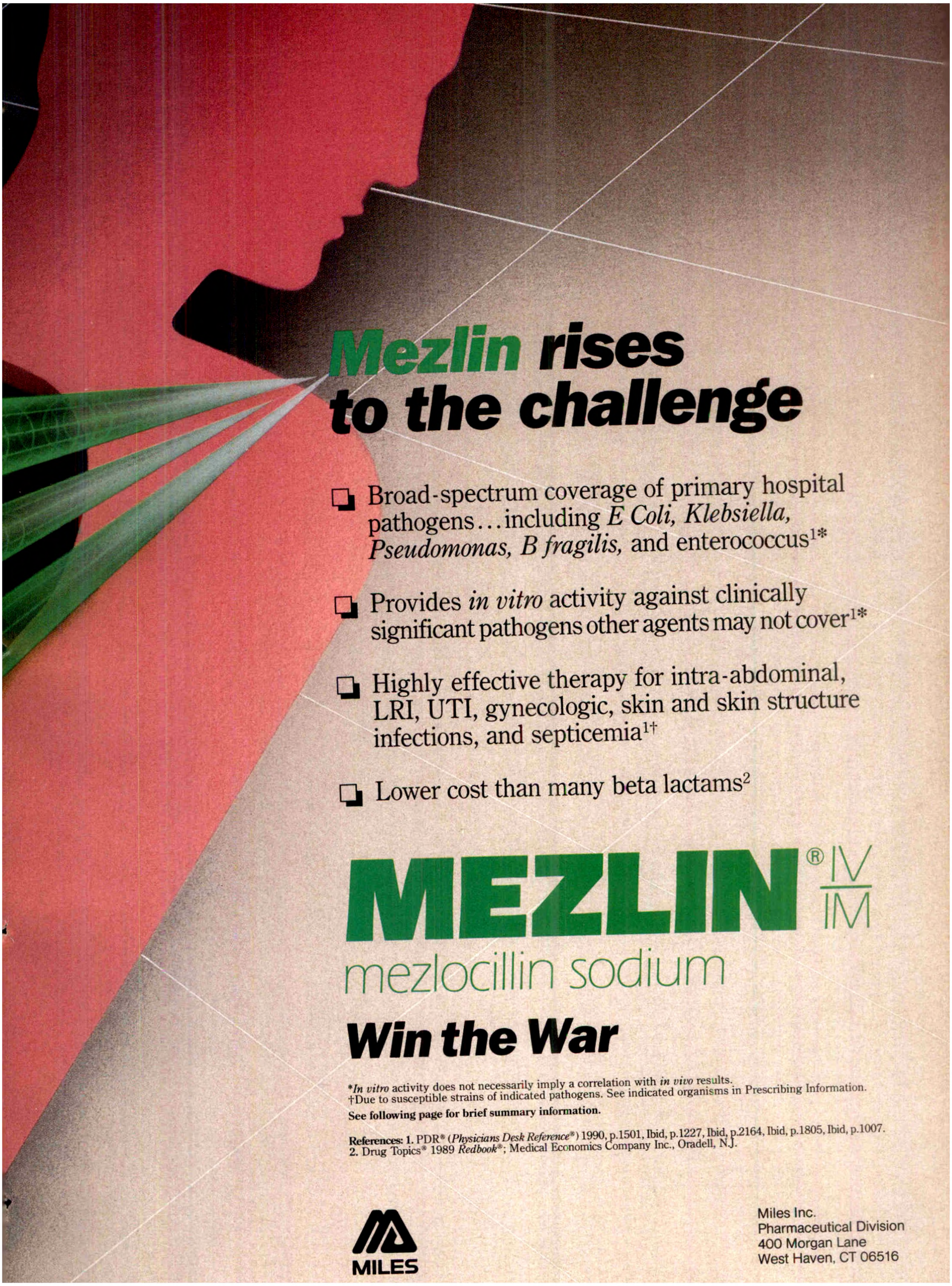

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See following page for brief summary information.

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INTRA-ABDOMINAL INFECTIONS including acute cholecystitis, cholangitis, peritonitis, hepatic abscess and intra-abdominal abscess caused by susceptible *E. coli*, *Proteus mirabilis*, *Klebsiella* species, *Pseudomonas* species, *S. faecalis* (enterococcus), *Bacteroides* species, *Peptococcus* species, and *Peptostreptococcus* species.

URINARY TRACT INFECTIONS caused by susceptible *E. coli*, *Proteus mirabilis*, the indole positive *Proteus* species, *Morganella morganii*; *Klebsiella* species, *Enterobacter* species, *Serratia* species, *Pseudomonas* species, *S. faecalis* (enterococcus).

Uncomplicated gonorrhea due to susceptible *Neisseria gonorrhoeae*.

GYNECOLOGICAL INFECTIONS including endometritis, pelvic cellulitis, and pelvic inflammatory disease associated with susceptible *Neisseria gonorrhoeae*, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species, *E. coli*, *Proteus mirabilis*, *Klebsiella* species, and *Enterobacter* species.

SKIN AND SKIN STRUCTURE INFECTIONS caused by susceptible *S. faecalis* (enterococcus), *E. coli*, *Proteus mirabilis*, the indole positive *Proteus* species, *Proteus vulgaris*, and *Providencia rettgeri*; *Klebsiella* species, *Enterobacter* species, *Pseudomonas* species, *Peptococcus* species, and *Bacteroides* species.

SEPTICEMIA including bacteremia caused by susceptible *E. coli*, *Klebsiella* species, *Enterobacter* species, *Pseudomonas* species, *Bacteroides* species, and *Peptococcus* species.

CONTRAINDICATIONS

MEZLIN is contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have occurred in patients receiving a penicillin. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with mezlocillin is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to penicillins, cephalosporins or other drugs. Antibiotics should be used with caution in any patient who has demonstrated some form of allergy, particularly to drugs.

If an allergic reaction occurs during therapy with mezlocillin, the drug should be discontinued. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT. EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD BE PROVIDED AS INDICATED.

PRECAUTIONS

Although MEZLIN shares with other penicillins the low potential for toxicity, as with any potent drug, periodic assessment of organ system functions, including renal, hepatic and hematopoietic, is advisable during prolonged therapy. MEZLIN has been reported rarely to cause acute interstitial nephritis.

Bleeding manifestations have occurred in some patients receiving betalactam antibiotics. These reactions have been associated with abnormalities of coagulation tests, such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal impairment. Although MEZLIN has rarely been associated with clinical bleeding, the possibility of this occurring should be kept in mind, particularly in patients with severe renal impairment receiving maximum doses of the drug.

MEZLIN has only rarely been reported to cause hypokalemia; however, the possibility of this occurring should also be kept in mind, particularly when treating patients with fluid and electrolyte imbalance. Periodic monitoring of serum potassium may be advisable in patients receiving prolonged therapy.

MEZLIN is a monosodium salt containing only 42.6 mg (1.85 mEq) of sodium per gram of mezlocillin. This should be considered when treating patients requiring restricted salt intake.

As with any penicillin, an allergic reaction, including anaphylaxis, may occur during MEZLIN administration, particularly in a hypersensitive individual.

As with other antibiotics, prolonged use of MEZLIN may result in overgrowth of non-susceptible organisms. If this occurs, appropriate measures should be taken.

Antimicrobials used in high doses for short periods to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhea should also be evaluated for syphilis. Specimens for dark field examination should be obtained from any suspected primary lesion and serologic tests should be performed. Patients treated with MEZLIN® should undergo follow-up serologic tests three months after therapy.

Interactions with Drugs and Laboratory Tests

As with other penicillins, the mixing of mezlocillin with an aminoglycoside in solutions for parenteral administration can result in substantial inactivation of the aminoglycoside.

Probenecid interferes with the renal tubular secretion of mezlocillin, thereby increasing serum concentrations and prolonging serum half-life of the antibiotic.

High urine concentrations of mezlocillin may produce false positive protein reactions (pseudoproteinurial) with the following methods: sulfosalicylic acid and boiling test, acetic acid test, biuret reaction, and nitric acid test. The bromphenol blue (Multi-stix®) reagent strip test has been reported to be reliable.

Pregnancy Category B

Reproduction studies have been performed in rats and mice at doses up to 2 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus, due to MEZLIN. There are however no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Mezlocillin crosses the placenta and is found in low concentrations in cord blood and amniotic fluid.

Nursing Mothers

Mezlocillin is detected in low concentrations in the milk of nursing mothers, therefore caution should be exercised when MEZLIN is administered to a nursing woman.

ADVERSE REACTIONS

As with other penicillins, the following adverse reactions may occur:

Hypersensitivity reactions: skin rash, pruritus, urticaria, drug fever, acute interstitial nephritis and anaphylactic reactions.

Gastrointestinal disturbances: abnormal taste sensation, nausea, vomiting and diarrhea. If diarrhea persists, pseudomembranous colitis should be considered.

Hematologic and Lymphatic Systems: thrombocytopenia, leukopenia, neutropenia, eosinophilia, reduction of hemoglobin or hematocrit, positive Coombs' test, and hypokalemia.

Abnormalities of hepatic and renal function tests: elevation of serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), serum alkaline phosphatase, serum bilirubin. Elevation of serum creatinine and/or BUN.

Central nervous system: convulsive seizures or neuromuscular hyperirritability.

Local reactions: thrombophlebitis with intravenous administration, pain with intramuscular injection.

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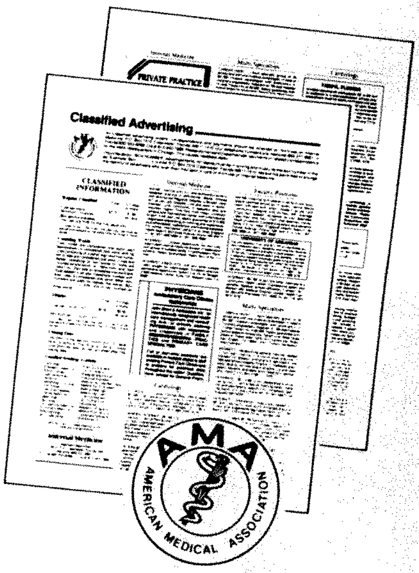

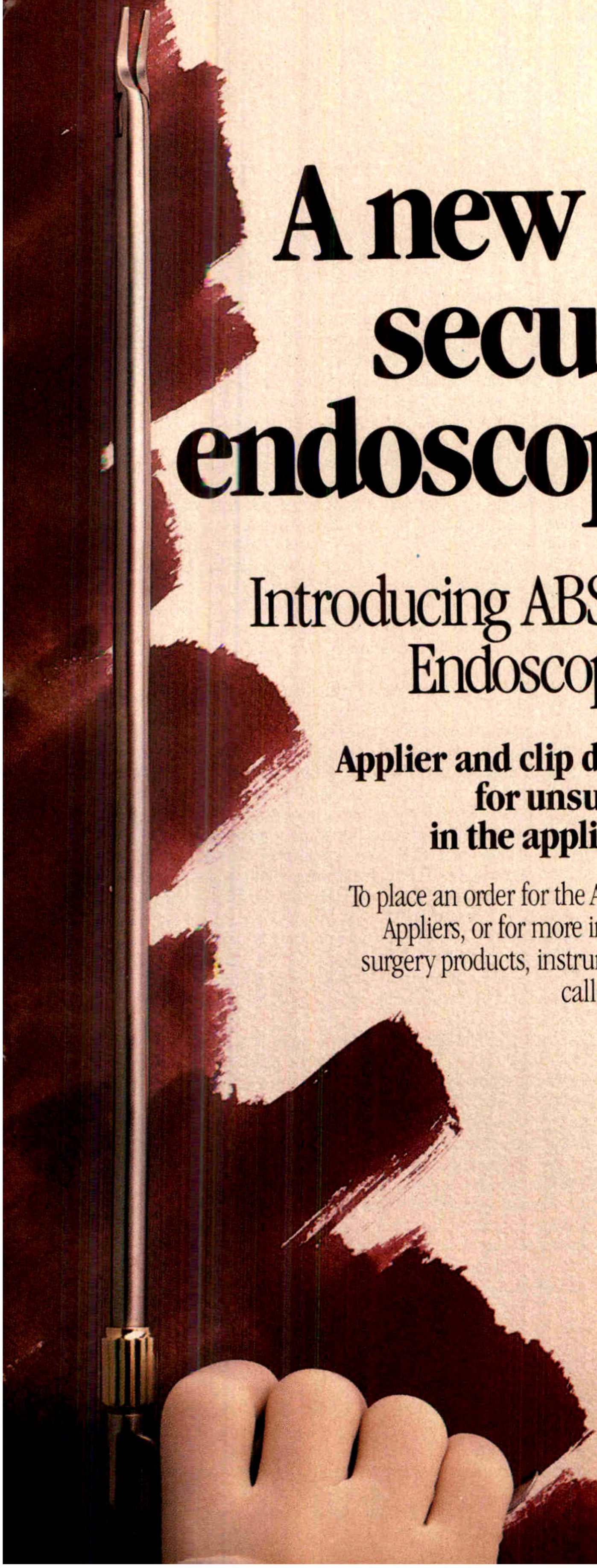

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Extracorporeal Membrane Oxygenation in the Treatment of Neonatal Respiratory Failure

Robert P. Foglia, MD; H. Scott Bjerke, MD; Robert E. Kelly, Jr, MD; J. Duncan Phillips, MD; Larry Barcliff, RRT; Eric W. Fonkalsrud, MD

• We report 18 consecutive neonates with severe respiratory failure due to pulmonary hypertension treated with extracorporeal membrane oxygenation. Extracorporeal membrane oxygenation was begun at 52 ± 36 hours of age with an arterial partial pressure of oxygen (Po_2) of 36 ± 14 mm Hg despite maximal pharmacologic and ventilator support (inspired fraction of oxygen [Fio_2], 0.99 ± 0.03; respiratory rate, 98 ± 31/min; and positive inspiratory pressure, 54 ± 11 cm of water). With initial flows of 130 ± 17 mL/kg per minute, ventilator settings were reduced to the following: Fio_2, 0.30; respiratory rates, 15/min; and positive inspiratory pressure, 24 cm of water. Support using extracorporeal membrane oxygenation was gradually reduced to 22% of initial flows and arterial blood samples showed pH 7.48 ± .05, Po_2 of 106 ± 27 mm Hg, and Pco_2 of 36 ± 5 mm Hg just prior to decannulation. After 107 ± 45 hours, extracorporeal membrane oxygenation was stopped and infants were extubated 61 ± 53 hours (median, 46 hours) afterward. There was one death (94.4% survival rate); all survivors were discharged and underwent a follow-up examination at 1 to 27 months of age. Complications included two intracranial hemorrhages (one death and one asymptomatic), one patent ductus arteriosis requiring ligation on extracorporeal membrane oxygenation, and chronic lung disease in one patient. In selected neonates, extracorporeal membrane oxygenation allows for resolution of pulmonary hypertension, results in improved survival, and is associated with a low incidence of chronic lung disease. Extracorporeal membrane oxygenation should be considered in the treatment of severe respiratory failure.

(*Arch Surg.* 1990;125:1286-1292)

Severe neonatal respiratory failure (RF) and associated pulmonary hypertension (PHN) has a mortality rate as high as 80%, despite the use of maximal ventilator and pharmacological support.[1-4] If the infant survives, there is a significant chance of the child developing bronchopulmonary dysplasia (BPD) because of treatment with high ventilator pressure and oxygen concentrations. Over the past several years, extracorporeal membrane oxygenation (ECMO) has been used to treat these infants and appears to afford increased survival.[5-8] However, there is still significant reluctance on the part of many neonatologists and pediatricians to use this treatment because of concerns regarding long-term survival, the effect of carotid artery and jugular vein ligation, and overall morbidity. To examine some of these questions we reviewed the experience at the UCLA Medical Center with the first 18 consecutive neonates undergoing ECMO because of severe RF, all of whom had failed maximal medical management.

PATIENTS AND METHODS

We treated nine boys and nine girls, all but one of whom were transported from other hospitals for management of their RF and PHN and consideration for treatment with ECMO. On arrival at UCLA, their care was managed by the attending neonatologists. Primary respiratory diagnoses included meconium aspiration syndrome (10 patients), primary PHN (4 patients), sepsis (2 patients), respiratory distress syndrome (1 patient), and pulmonary hemorrhage (1 patient). All neonates had high respiratory rates (RRs), inspiratory pressure, and inspired fraction of oxygen (Fio_2) when transferred. Management consisted of induced respiratory alkalosis, alkalinizing agents used to raise the serum pH, and hyperventilation, in an attempt to reverse the pulmonary vasospasm. Maximal pharmacologic management consisted of sedation and muscle relaxants in all cases. At least one systemic vasopressor (dopamine or dobutamine) was also used in every case. Tolazoline hydrochloride was used in nine neonates in an attempt to achieve pulmonary vasodilatation. Neonates were 40 ± 3 weeks' gestational age and weighed 3.42 ± 0.57 kg at birth. At the time ECMO was started, infants had gained 11% ± 4% of their birth weight. Their age at the start of ECMO was 52 ± 36 hours. All values are reported as means ± SDs.

Criteria for ECMO are listed in the Table. Respiratory failure criteria included the use of alveolar arterial oxygen difference ($AaDO_2$) and/or oxygenation index. This was calculated using the following equation:

$$AaDO_2 = \text{Barometric Pressure (760 mm Hg)} - \text{Water Vapor Pressure (47 mm Hg)} - (Po_2 + Pco_2)$$

The oxygenation index equals Fio_2 times Po_2 divided by mean airway pressure. Others have shown that in neonates, an $AaDO_2$ that is greater than 610 mm Hg for 8 hours, or an $AaDO_2$ that is greater than 605 mm Hg with a positive inspiratory pressure (PIP) that is greater than 38 cm of water for 4 hours predicted a mortality greater than 80%.[3] Likewise, an oxygenation index greater than 0.40 is associated with a similar mortality. When a decision was made that a child had failed maximal ventilator and pharmacologic management, ventilator settings averaged as follows: RR, 98 ± 31; Fio_2, 0.99 ± 0.03; positive inspiratory pressure (PIP), 54 ± 11 cm of water; and peak-end expiratory pressure (PEEP), 2 ± 1 cm water. Resulting arterial blood gas values were as follows: pH, 7.43 ± 0.19; Po_2, 36 ± 14 mm Hg; and Pco_2, 37 ± 14 mm Hg. Calculated $AaDO_2$ averaged 640 ± 13 mm Hg, with a range of 617 to 659 mm Hg, and the oxygenation index was 0.61 ± 0.22.

Prior to ECMO, a cranial ultrasound examination yielded normal results in all neonates. Cardiac echo studies showed no structural cardiac pathology to account for the hypoxia. A patent ductus arteriosis (PDA) and often a patent foramen ovale was identified and a right-to-left shunt documented. Standard venoarterial ECMO was begun with cannulation of the right atrium via the right internal jugular vein with a 10F to 14F cannula, and cannulation of the aortic arch via the right common carotid artery with a 10 F cannula. The bypass circuit has been described previously.[5] This procedure was always an emergency procedure and often was performed at the time of progressively worsening hypoxia and blood pressure instability. One child had been resuscitated from a cardiopulmonary arrest shortly before cannulation.

Priming volume of the ECMO circuit was approximately 425 mL and consisted of a balanced crystalloid solution, packed red blood cells, and albumin. The albumin used in the prime was 7.5 grams in the first two patients and 15 g in the last 16 patients. The blood volume of an infant weighing 3.4 kg was approximately 270 mL, resulting in approximately 1.5 times more blood outside of the neonate than in its cardiovascular system. Systemic heparinization of the neonate was carried out with an average of 250 U/kg of heparin given by bolus. An activated clotting time (ACT) was checked five minutes

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later and vessel ligation and cannulation performed when the ACT was greater than 400 seconds.

RESULTS

Flow of ECMO was started at 50 mL/min, and progressively increased by 50-mL increments each minute until a flow of approximately 120 mL/kg per minute was achieved, which was felt to be approximately 75% of the total cardiac output. Within 5 to 8 minutes of starting bypass, pulse oximetry showed oxygen saturation greater than 95%, arterial Po_2 was 75 to 90 mm Hg and Pco_2 was 35 to 45 mm Hg in almost all cases. Ventilator settings had been reduced to "rest" settings: Fio_2, 0.30; RR, 15/min; and PIP, 24 cm of water. Ventilator PEEP was placed at 4 cm of water in the first two patients, and at 14 cm of water in the last 16 patients. In the latter group, PEEP was gradually reduced from 14 to 4 cm of water beginning when ECMO flow was decreased to 70 mL/kg per minute.

Systolic blood pressure often would rise and vasopressor support could usually be stopped within 10 minutes of starting ECMO. Pulse pressure on ECMO consistently fell as the ratio of ECMO to non-ECMO flow increased, since ECMO flow was nonpulsatile. As ECMO flow was decreased, pulse pressure would again widen. Continuous infusion intravenous fentanyl was used for sedation and blood pressure control, and was begun in all patients at a rate of 1 µg/kg per hour. Systolic hypertension (greater than 90 mm Hg) was frequently noted during the first 30 minutes of ECMO and was treated by increasing the fentanyl infusion rate. It then often resolved, and the fentanyl could be decreased to 1 to 2 µg/kg per hour. During the total time of ECMO, the fentanyl required to control blood pressure and for sedation increased by 12.6 ± 7.0 times.

Anticoagulation was controlled by the use of continuous-drip heparin, titrated based on ACT values checked at least hourly. Heparin utilization averaged between 35 and 45 U/kg per hour. The ACT values were within 20 seconds of the desired value 81% of the time. After the continuous-drip heparin was started, ACT values were greater than 300 seconds only 1.3% of the time, and a heparin bolus was needed to treat an inordinately low ACT only 1.5% of the total time on bypass.

As the PHN resolved, more venous blood would pass from the right heart and pulmonary artery to the lungs rather than through a right to left shunt. Flow of ECMO was progressively reduced by 10-mL increments every 1 to 2 hours, based on arterial and venous blood gas levels until a flow of 100 mL/min was reached. This was approximately 30 mL/kg per minute, or about 20% of the infant's total cardiac output. If this was well tolerated for 4 hours, ECMO was then discontinued.

The average length of cardiopulmonary support with ECMO for these patients was 107 ± 41 hours. Our first two patients underwent ECMO for a total of 405 hours. If they were excluded from the study, our next 16 consecutive patients underwent ECMO for only 95 ± 22 hours. There were 17 patients who no longer required treatment with ECMO (94.4% ECMO survival rate). When ECMO was stopped, patients were initially maintained with the following ventilator settings: Fio_2, 0.40 ± 0.12; RR, 21 ± 7/min; and PIP, 24 ± 4 cm of water. They required ventilator support for only 61 ± 53 hours (median, 46 hours) after decannulation and were then extubated. These neonates were breathing room air with no supplemental oxygen a median of 5.3 days after discontinuation of ECMO.

Patients remained at UCLA Hospital for a total of 11.8 ± 6.0 days, and their median total hospitalization after the start of ECMO was 25 days. All survivors were discharged and have had follow-up examinations after 1 to 27 months (median, 12 months); there have been no late deaths; thus the long-term survival rate is also 94.4%. Of the 17 survivors, all are normal or near normal. No child has any major or minor neurologic abnormality. One child had BPD and required supplemental oxygen for 3 months, but no longer requires this. Another child underwent tracheostomy for bilateral vocal chord paresis thought to be caused by endotracheal tube trauma. There has been no case of sepsis in over 1900 hours of ECMO support.

Criteria for Treatment With Extracorporeal Membrane Oxygenation

- Gestational age ≥35 wk
- Weight >2 kg
- No structural cardiac disease
- No intracranial hemorrhage
- No severe coagulopathy
- Less than 7 d of assisted ventilation (relative limit)
  or <10 d of assisted ventilation (absolute limit)
- Maximal ventilator management
- Respiratory failure criteria

Morbidity and Mortality

There was one death during ECMO among the 18 patients (94.4% survival rate). Because of the concern in regard to intracranial hemorrhage, all neonates underwent daily cranial ultrasound examinations while receiving ECMO and a computed tomography or magnetic resonance imaging study within 2 weeks of discontinuation of ECMO. Two neonates (11.1%) suffered an intracranial hemorrhage, both documented by ultrasound study. Complications also included neck wound bleeding, requiring exploration in one patient; BPD in one patient; bilateral vocal chord paresis in one patient; and a PDA requiring ductal ligation. Two patients had seizure activity noted prior to arrival at UCLA. No seizure activity or any evidence of neurologic dysfunction was seen in any patient either while receiving ECMO or subsequently.

The only death in the series was that of a 2.7-kg infant who suffered a grade IV intracranial hemorrhage. The child was admitted with severe PHN and RF due to sepsis, and had renal failure, arterial Po_2 less than 40 mm Hg, and systolic blood pressure less than 40 mm Hg for 12 hours prior to transfer despite transfusions with 70 mL/kg of colloid solution. The neonate began receiving ECMO, and despite the use of multiple diuretics, increased its weight by 32%, and continuous arterial venous hemofiltration was begun. A cranial ultrasound examination on the third day showed a grade IV hemorrhage. The child could not be managed on a ventilator alone without ECMO support. Because of the large ICH, ECMO was discontinued, and the child died shortly thereafter. One other patient had a small grade I germinal matrix intracranial hemorrhage. She was gradually weaned off ECMO during a 48-hour period and was totally asymptomatic both during ECMO and subsequently. One patient had BPD, defined as requiring supplemental oxygen at greater than age 28 days. This patient was our oldest at the time of starting ECMO, and underwent bypass at 165 hours of life after 7 days of ventilator management with high oxygen concentrations and pressures. He was receiving Fio_2 at 0.88, the only patient not receiving 100% oxygen prior to ECMO, but he required a PIP of 60 cm of water. After ECMO he required supplemental oxygen for the first 3 months of life and was hospitalized for 4 months.

Another patient with RF due to sepsis developed a marked persistent left-to-right shunt through a PDA. Serial cardiac echo studies demonstrated that flow through the PDA changed progressively from right-to-left shunting, to bidirectional shunting, to left-to-right shunting as the PHN resolved. Despite fluid restriction, the PDA did not close and the chest roentgenogram showed an enlarged heart size and pulmonary edema at day 9 on ECMO. A left thoracotomy and PDA ligation was performed while the child was heparinized and receiving ECMO. The lung hyperemia resolved within seconds after the ductus was closed, and a chest roentgenogram taken 4 hours later showed a marked decrease in heart size, and resolution of the pulmonary edema. The procedure allowed for the ECMO flows to be rapidly decreased, and 30 hours after PDA ligation, the infant could be taken off ECMO.

Chest Roentgenograms

The chest roentgenograms prior to ECMO were variable in pathology and included four patients (22%) who had evidence of barotrauma. A chest roentgenogram was obtained in all infants shortly after starting ECMO. These films were of interest because in a number of cases, despite excellent arterial oxygen saturations, the lung fields had a dense interstitial infiltrate pattern. The first two patients in the series developed a global interstitial edema pattern or lung "white-out" shortly after being placed on ECMO (Fig 1, top and center). This pattern often took several days to clear. At the conclusion of ECMO, the chest roentgenogram showed complete resolution of the process (Fig 1, bottom). Subsequent patients were managed with both higher levels of colloid oncotic pressure in the ECMO circuit and high levels of PEEP, and the degree of interstitial edema declined in a number of cases (Fig 2). These infants required less ECMO flow soon after bypass was started, indicating the probability of blood flow to the lungs and gas exchange. In several infants, this was confirmed by cardiac echo showing bidirectional or left-to-right shunting soon after ECMO was begun. In general, improvements in pulmonary gas exchange were associated with progressive resolution of air bronchograms, clearing first in the peripheral lung field and later centrally, and an improved pulmonary compliance manifested by the diaphragms at a lower level on chest roentgenogram and increased chest rise on clinical examination. Only one patient (6%) was found to have evidence of BPD after completion of ECMO.

Metabolic

The average weight of infants shortly after starting ECMO was 11%±4% above birth weight. The neonates clinically appeared edematous, and their chest roentgenograms often corroborated the clinical findings of fluid overload. Patients were managed with fluid restriction to 80 to 90 mL/kg per day. The use of a diuretic, either furosemide or ethacrynic acid, was helpful in instituting a brisk diuresis of 3 to 4 mL/kg per hour. Only one patient developed renal failure and required hemofiltration. As the neonates began to lose this excess weight, if edema was present, the lung fields on serial radiographic examination showed progressive clearing. Concomitant with this, the arterial Po_2s improved, and we could begin to reduce the amount of ECMO support. Neonates were decannulated when their weight had decreased to approximately 3% above birth weight, or approximately 6% to 7% above what their ideal weight should be at approximately age 6 days.

While on ECMO, neonates received total parenteral nutrition infused directly into the circuit. Administration of 2% amino acids, and 10% dextrose was started, and dextrose concentration was increased by 5% each day. Administration of lipids at 20% concentration was started at 1 g/kg per day and increased over 2 days to 3 g/kg per day. Total parental nutrition made up almost 65% of the total fluid intake, and we ultimately could deliver approximately 378 to 399 J/kg per day to these infants. A metabolic alkalosis was consistently seen;

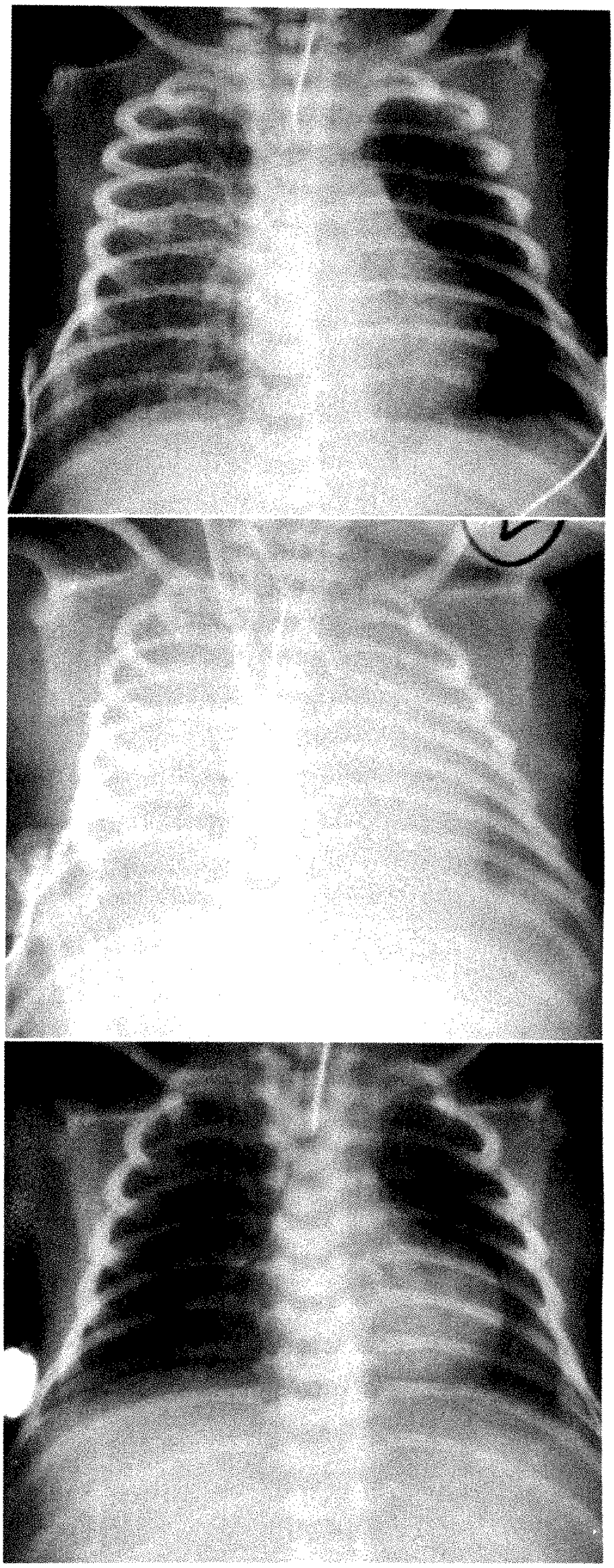

Fig 1.—Top, Chest roentgenograms of patient 2 with severe respiratory failure prior to ECMO. Note the relatively clear lung fields. Center, Patient 2, 1 hour after starting ECMO treatment. Significant interstitial edema noted. Bottom, Patient 2 after 1 week of ECMO treatment and shortly after decannulation with complete resolution of interstitial edema.

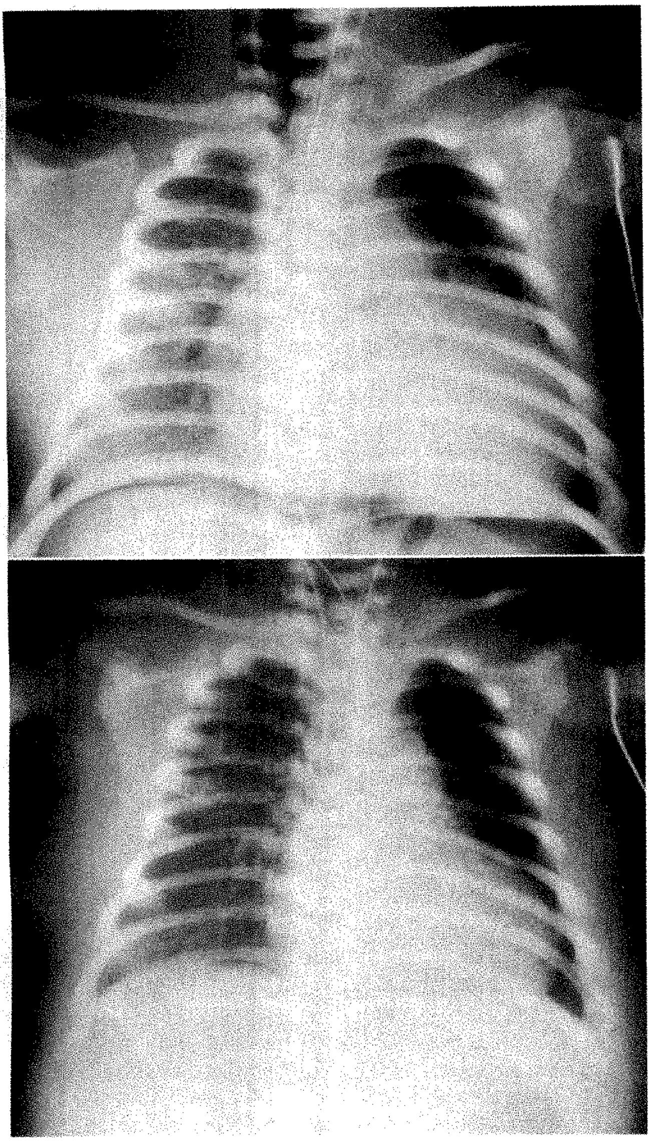

Fig 2.—Top, Chest roentgenogram of patient 12 just prior to ECMO. Note pneumoperitoneum due to high ventilator pressures. Bottom, Patient 12, 1 hour after ECMO treatment was begun. Note lack of interstitial edema and peritoneal tube evacuation of pneumoperitoneum.

it was highest during the initial stages of ECMO and then gradually decreased. Sodium requirements in infants receiving ECMO averaged 2 mmol/kg per day, one half the normal amount. In contrast, potassium requirements were often 4 to 5 mmol/kg per day, roughly 2 to 2.5 times normal.

COMMENT

At present, ECMO is no longer considered experimental therapy, but remains a form of rescue therapy for neonates with severe PHN that is unresponsive to maximal ventilator and pharmacologic treatment. Despite over 3000 neonates treated with ECMO, and an 82% ECMO rate of survival,[9] significant skepticism and reluctance still exists in the minds of many neonatologists and pediatricians. This skepticism is based on several concerns: (1) the validity of the defined RF criteria[10]; (2) the long-term survival vs survival on ECMO alone; and (3) the overall morbidity.

A number of ECMO centers have used the data of Bartlett et al[11] and Short et al,[3,12] who retrospectively reviewed neonates with severe RF in the early 1980s and defined an 80% mortality based on $AaDO_2$ or certain levels of pH, Pco_2, and barotrauma. The question of validity of the use of "historic" data from management 7 or more years ago was raised by Dworetz et al.[13] They applied these criteria to patients at Yale New Haven (Conn) Hospital from 1980 to 1981 and found an accurate prediction of mortality; in contrast, when these criteria were applied to patients between 1986 and 1988, the mortality rate was only 11%. The management of PHN has improved markedly over the past decade, and it is likely that a higher $AaDO_2$ value is needed to predict poor outcome. Recently, O'Rourke et al[6] carried out a randomized prospective trial in neonates with severe RF and PHN; they found a 97% overall survival rate in the ECMO-treated group in contrast to a 60% survival rate in patients treated with conventional medical therapy.

In our study, the average $AaDO_2$ of patients treated with ECMO was 640 ± 13 mm Hg. This value is greater than two SDs higher than the $AaDO_2$ value of 605 mm Hg from patients in the studies by Short et al[12] and Beck et al,[3] and we feel encompasses a group of patients who are truly critically ill. Likewise, our oxygenation index value of 0.61 ± 0.22 is greater than the value of 0.40 used by others to define an 80% mortality.

In a practical sense, we could not manipulate the relative severity of the RF. The neonate's care was governed by the neonatology staff. The ECMO service treated the child only after the neonatologists felt that they had exhausted all other forms of therapy and that the child was likely to die unless some other treatment was available. The only patient who was not at "maximal" ventilator settings was a 3.1-kg infant with meconium aspiration syndrome who had been on a ventilator for almost 7 days, had been weaned to an Fio_2 of 0.88, an RR of 30/min and pressure settings of 60/4 cm of water, with an arterial Po_2 of 56 mm Hg and Pco_2 of 33 mm Hg. He was started on ECMO because he could not be weaned further and was at the outer limit of ECMO candidacy because of the extended length of time on a ventilator. Although he had a relatively short course of ECMO, he proved to be the only patient who developed chronic BPD; he required supplemental oxygen for 95 days and was hospitalized for 120 days.

The second issue is that of long-term survival. Although the survival rate of patients receiving ECMO is 82% nationally, this does not address the mortality rate in the hospital after ECMO, or the long-term survival. Weber et al[14] reported an 86% ECMO survival rate, but they also listed four subsequent hospital deaths during the next 60 days that lowered the rate of survival to 68%. Bartlett et al[5] reported seven late deaths in 72 ECMO survivors (10% incidence) due to causes such as unresolved BPD, severe brain damage, and cardiac damage. A major factor accounting for the discordance between ECMO survival and in-hospital and long-term survival may be the consequences of hypoxia and ventilator injury in a number of patients. Improved methods of performing ECMO, along with using it more promptly in the treatment of neonates with RF, should result in little difference between ECMO, in-hospital, and long-term survival rates. The present study shows no difference between ECMO, in-hospital, and long-term survival rates; it is 94% in each case.

There has also been great concern regarding the morbidity associated with ECMO. The Extracorporeal Life Support Organization Registry data show a 16% incidence of ICH, seizures in a similar number of patients, and other neurologic sequelae occurring with an incidence of 3.1%.[9] This concern deals with the issue of cerebral perfusion, hypoxia, and the dangers, both proximate and longitudinal, of right common carotid artery and internal jugular vein ligation. Furthermore, questions have been raised about the risk of bleeding with long-term (4 to 6 days) heparin therapy in newborns, and the morbidity associated with mechanical complications with the circuit-oxygenator, heat exchanger failure, tubing rupture, clot formation, and air emboli.

Over the past 5 years, ECMO has gone through an evolution, with new centers increasing and the number of new patients growing by at least 50% each year. Because of the pioneering work of Bartlett and his associates, ECMO is much safer now than it was 5 years ago. The equipment has improved and the number of mechanical problems has declined.[9] The training of personnel has also improved. Most importantly, the focus of our attention now is not simply on maintaining a patient on cardiopulmonary bypass for 4 or 5 days. Rather, fundamental questions are being asked regarding the effects of long-term bypass and nonpulsatile flow on organ perfusion, the pathophysiology of neonatal hypoxia, the significance of reoxygenation injury, the effects of ECMO on intracranial perfusion dynamics, the resolution of pulmonary vasospasm, and the recovery of lung function. In this way, strategies can be developed to optimize the manner in which ECMO is carried out, with the end result being a shorter and safer course of ECMO.

The changes in physiology with ECMO are major as evidenced by the profound changes in fluid and electrolyte balance requirements. At least two mechanisms account for the metabolic alkalosis seen in this study: the metabolism of citrate from the blood used for the pump prime, and an aldosterone effect, possibly related to the degree of nonpulsatile flow to the kidneys. Increased aldosterone would account for sodium resorption, and potassium and hydrogen excretion in the distal convoluted tubule of the kidney, as well as a concomitant aciduria seen in a number of these patients.

A paradox of ECMO is that one of the major causes of mortality and morbidity is an intracranial accident, rather than irreversible cardiac or pulmonary damage. Our hypothesis is that the combination of the posthypoxic state, the inhomogeneity of cerebral blood flow due to common carotid and internal jugular ligation, and anticoagulation, along with hypertension, create an environment with increased potential for bleeding. Our laboratory has previously shown a 39% decrease in right- vs left-sided cerebral perfusion pressure in posthypoxic neonatal lambs receiving ECMO. However, the pressure drop across the collateral circulation progressively improves, so there is only a 9% perfusion pressure difference after 36 hours of ECMO.[15] This may indicate a relatively low risk for neurologic problems to occur subsequent to ECMO.

Sell et al[16] have reported a 52% incidence of ICH and associated this with systolic hypertension. Careful control of blood pressure and the ACT level may help to decrease ICH. Infants are probably at greatest risk for ICH during the first 24 hours of ECMO, the immediate posthypoxic period when the cerebral capillary membrane is most unstable. Systolic hypertension is commonly seen during the initiation of ECMO and may be caused by calcium flux, volume loading with increasing preload, a relative lack of autoregulation, or not rapidly tapering the vasopressors that the neonates are often receiving. The use of fentanyl has aided in keeping the systolic pressure less than 90 mm Hg during this time when the ACTs are often in the 400- to 500-second range.

Maintenance of well-controlled anticoagulation with no large fluctuation in ACT values should decrease the risk of not only ICH, but also gastrointestinal, genitourinary, and pulmonary bleeding. We have shown that ACTs can be maintained within 20 seconds of the desired level for more than 80% of the time. With ACTs maintained at 220 to 240 seconds, we noted two cases (11.1%) of ICH; no patient with seizures; one neck wound requiring exploration for bleeding; and no gastrointestinal, genitourinary, or pulmonary hemorrhage. There have been no problems related to fibrin clot formation or oxygenator failure.

The development of pulmonary interstitial edema has been a common problem in patients undergoing ECMO. The causes of this diffuse interstitial edema may be due to a reperfusion or reoxygenation injury to the lung. At least two components of Starling's law of fluid flux can contribute to this: colloid oncotic pressure and a membrane injury with a change in the capillary membrane constant. Moront et al[17] have reported excellent success in 50 neonates treated with ECMO and high levels of PEEP. These neonates were able to have ECMO discontinued more than 29% faster than a comparable group of neonates treated with ECMO and low levels of PEEP. The use of high levels of PEEP is felt to counteract the capillary leak in the lung by raising the interstitial hydrostatic pressure.

We speculate that the components of the pump prime are also integral to the development of edema and overall fluid retention. Previously, only sufficient albumin had been added to the pump prime to coat the membrane lung to decrease platelet aggregation. However, this could result in a serum albumin in the circuit of less than 20 g/L. Our first two patients both suffered white-out of the lungs and had an aggregate 405 hours of ECMO. Starting with our third patient, we have routinely primed the circuit with 15 g of albumin. Serum albumin levels measured after starting ECMO have consistently been greater than 30 g/L. This increase in colloid oncotic pressure in the capillary space, combined with the increase in interstitial hydrostatic pressure due to the high PEEP, may counteract some of the fluid flux out of the capillary space into the interstitium. Using these strategies in our last 16 consecutive patients, time on ECMO has averaged 95 hours, a 21.5% decrease from the national average.[9]

By decreasing complications while administering ECMO, the length of bypass should be shortened, and may be associated with both increased survival rates and an improved quality of life. The decrease from an ECMO survival rate of 80% to 85% to a long-term survival rate of 65% to 70% in previous studies was often due to late sequelae of a neurologic or pulmonary injury. If the complications are decreased during ECMO, there will be fewer long-term problems. We have been gratified to find a relatively low complication rate of ECMO and a subsequent excellent long-term survival rate of 94%.

We believe that ECMO clearly plays an essential role as a life-saving rescue technique for critically ill infants with PHN. It has progressed to a point where a relatively new center such as ours can carry out this type of treatment with an excellent rate of survival. An examination of not only survival statistics, but the relatively low risk of morbidity, raises the question of what the role of ECMO should be in the next several years. Some element of the neurologic complications in infants treated with ECMO was not caused by ECMO alone, but was the result of the profound hypoxic insult the child had suffered during the period of RF and PHN, and exacerbated perhaps by the ventilator management. Perhaps consideration should be given to earlier intervention with ECMO in two types of patients. The first would be the extremely poorly oxygenated neonate, for whom ECMO would decrease the risk of a cerebral hypoxic injury. The second group is that comprising infants who have, at best, marginal oxygenation but at the expense of high FiO_2 and extremely high ventilator pressures. It may be that rather than languishing for weeks to months on a ventilator, those neonates would benefit from treatment with ECMO. More prompt consideration of its use in selected infants may afford an even smaller risk of mortality and morbidity than we report presently.

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Discussion

DAVID TAPPER, MD, Seattle, Wash: Extracorporeal membrane oxygenation is a labor intensive state-of-the-art form of respiratory therapy. The goals of this technique are to (1) provide appropriate oxygenation and carbon dioxide elimination at minimal distending pressures; (2) minimize oxygen toxicity and barotrauma; and (3) stabilize the swings in oxygenation during periods of pulmonary hypertension related to persistent fetal circulation. The authors report a standard approach with quite acceptable results. There are currently 63 centers using this technology and, as of October 1989, 2946 patients have been entered in an ECMO registry. In the categories that the authors list under respiratory failure, there have been 1161 patients with meconium aspiration with a 92% survival rate, 419 patients with primary pulmonary hypertension with an 87% survival rate, and 337 patients with sepsis with a 77% survival rate.

It is important to consider a number of things. Have the authors evaluated the long-term sequelae of ligating the common carotid artery? Do you favor reconstruction of the common carotid at the time of decannulation and why? Would it be possible to use this technology without heparinizing the patients? Specifically, is there a role for heparin-bonded catheters or venovenous bypass? What is on the horizon? Will you extend this technology to older infants and children with respiratory failure?

GEORGE G. LINDESMITH, MD, Los Angeles, Calif: At the Childrens Hospital, Los Angeles, Calif, the ECMO program is directed by Jim Atkinson, MD. We have 135 cases with a 13% mortality rate. The distribution of our cases is not different from the national average. Our data support the authors' contention that this is a very useful modality. Our experience with the use of ECMO in neonates with congenital heart disease has included five patients. All five were successfully weaned from ECMO following repair of their cardiac defects, and of the group, there were two long-term survivors.

We have used it as a sort of bridge to cardiac surgery in those patients who were so critically ill and dying that to subject them to surgery would have resulted in 100% mortality. If we stabilize these patients with ECMO, take them to the operating room with the ECMO circuit in place, and then perform cardiac surgery, we do get some long-term survivors.

My question to the authors is, do they have experience with, or comments regarding, this expansion of the use of this modality?

PAUL W. JOHNSTON, MD, Pasadena, Calif: Since May 1985, the ECMO program of the Neonatal Department at the Huntington Memorial Hospital, Pasadena, Calif, under the direction of R. Liberman, MD, E. Gangitano, MD, and J. Vogt, MD, has treated 228 patients, with a 28-day survival of 95% and a 1-year survival of 87%.

Since the patient receiving ECMO must be anticoagulated with heparin, bleeding is the most frequent complication of the procedure, either from the various operative sites or within the cranium. In 55 patients at the Huntington Memorial Hospital, a double venous cannulation has been used with a cephalad and a caudad catheter in the internal jugular vein. Since 20% of the venous return to the heart comes from the head, the cephalic vein catheter is placed to reduce the cerebral venous congestion. Preliminary unpublished results show that there is less plethora of the skin of the head and neck, less bleeding from the operative wound of the neck, and fewer episodes of intracranial bleeding, particularly in the group of gestational age 34 to 36 weeks. What measures do you use or consider to control the complication of bleeding?

Of particular interest to the pediatric surgeon is the role of ECMO in the surgical repair of congenital diaphragmatic hernia, and whether ECMO can alter the high mortality when such hernias are diagnosed and treated in the first 24 hours of life. The high mortality is related to pulmonary hypoplasia and the persistent pulmonary hypertension. The crux of the matter is how quickly some of these structural and functional problems can be reversed by ECMO. Another problem to consider is that surgical repair of the diaphragmatic hernia decreases the compliance of the lungs, and can temporarily make the pulmonary vascular resistance worse.

Certain questions are as yet unanswered. (1) Is there a degree of pulmonary hypoplasia that precludes survival, no matter how the patient is treated? How do you select these patients? (2) Have you found that the carbon dioxide ventilation index of Bohn predicts with any degree of accuracy the survivor and nonsurvivor of ECMO? (3) Should the repair of the congenital diaphragmatic hernia be done before, during, or after the ECMO, and how do you decide?

ALFRED A. DELORIMIER, MD, San Francisco, Calif: This modality should be introduced much earlier in the course of the patient's care and particularly when it becomes necessary to use vasopressors. We have had real problems cannulating the vena cava and innominate vein when vasoconstrictors, such as norepinephrine, have been used. It is desirable to use as big a catheter as possible use to achieve adequate venous drainage, and when the vessels are clamped down to a thread it is a real technical challenge to cannulate the vessel. So we now ask our neonatologists to call us when they get to a point where they are having to use vasopressors.

We have now reconstructed the carotid artery in six neonates. All of the vessels have remained open by Doppler study afterward and I think this will help nullify the concerns of the neonatologists and pediatricians about the long-term outcome of these children.

One of the criteria for exclusion from the use of ECMO was the presence of cardiac disease, but I support Dr Lindesmith's premise that ECMO should be used for selected infants with cardiac disease. We just had an infant with total anomalous pulmonary veins, and ECMO admirably rectified the neonate's severe metabolic problems, and the anomalous venous drainage could then be fully corrected within a couple of days after beginning on ECMO.

JOHN R. BENFIELD, MD, Sacramento, Calif: The enthusiasm for ECMO that has been expressed herein, and which I share, is not shared unanimously. There are people who believe that methods of nonoperative respiratory support have improved enough so that controls are extremely important.

I am reminded of my early experience in lung transplantation, when I offered lung transplantation to a patient nearly 20 years ago. She initially accepted and then decided not to have the operation and for many years, until recently, she was the "longest surviving lung transplant recipient." How secure are the selection criteria for ECMO, and how suitable are the controls? Do future studies need to include controls managed by the best available nonoperative means?

FRANK R. LEWIS, JR, MD, San Francisco: Do you think the development of interstitial edema after beginning ECMO might be due to a relaxation of the pulmonary vasoconstriction that is present while patients are hypoxic but that is relieved when they begin ECMO therapy? You did not discuss that in the presentation, and I wonder if you have investigated it by looking at changes in pulmonary vascular resistance?

In adults, pulmonary hypertension does not go away at the time they are weaned from ventilators, but remains as a long-term problem due to anatomic changes. Even when infants are weaned and oxygenation improves, does the pulmonary hypertension actually go away, or is it still present at the time they are weaned?

Adults who are on a ventilator for a long time lose exchangeable capillary surface area irreversibly. Have these children had long-term follow-up in regard to their development and long-term respiratory function?

You indicated that high PEEP levels might help to resolve the edema. In the available physiologic studies both in humans and animals, the application of PEEP has been found either to have no effect or to increase the edema. Why do you think it might be different in infants?

DR FONKALSRUD: Dr Tapper, heparin-bonded catheters are certainly under study for use in the ECMO circuit. If we do not have to use heparin, the overall success of the procedure will be enhanced and the incidence of intracranial hemorrhage will most likely be reduced. Work is under way to study the application of ECMO to older patients. Application to infants weighing less than 2 kg is still complex, but is under extensive study.

We concur that ECMO may, on occasion, supplement the postoperative care following repair of difficult congenital cardiac anomalies.

DR FOGLIA: For 5 or 6 years work has been done to get heparin bonding for the children's circuits. In Sweden, they have used the Carmeda system that works well in the animal model, and they are beginning to use this system in humans to avoid the issue of heparin.

The risk of intracranial hemorrhage is not only related to the use of anticoagulation, but goes back to the primary problem: the hypoxia in these infants and the cerebral capillary membrane instability.

My bias is that ECMO may cause some degree of reoxygenation injury. It is not really reperfusion injury, but more of a reoxygenation injury, and certain strategies try to decrease that risk. One strategy might be the use of superoxide dismutase and catalase, and some people have been evaluating use of calcium-channel blockers in infants.

Reconstruction of the carotid artery can be done in pediatric surgery. There has been a reluctance to do this because of the risk of platelet aggregation on the suture line with embolization intracranially.

When we carry out ECMO, we obviously produce a significant change in physiology. If we have an infant who is hypoxic, we ligate the vessels. We use a nonpulsatile flow, and we have inhomogeneous flow. We looked at this issue in a series of newborn lambs. They were made hypoxic, put on a ventilator, and for 3 hours were kept at a P_{O_2} of 30 to 35 mm Hg. We compared them with a series of normoxic lambs. Both groups were started on ECMO therapy and an oculopneumoplethysmography (OPG) technique was used to evaluate pressures in the right and left eyes as a manifestation of right and left intracranial perfusion pressure.

We measured the right and left OPG ratio in the hypoxic animals within 1 hour of going on bypass and found a significant depression, a 39% depression in right hemispheric perfusion. When ECMO therapy was continued in these animals, we found a stepwise improvement in OPG so that 18 hours after being on ECMO, the OPG ratio in the hypoxic animals returned to 92%, or only 8% asymmetry. We think that this speaks to what the risk is longitudinally after coming off ECMO therapy because of the carotid ligation.

Reconstruction of the carotid may obviate the whole issue, but we think that there is not a sufficient risk if the neonate completes ECMO therapy. As far as I know, no infant who has been off ECMO therapy has developed a later complication, but the oldest of these patients is now only 14 years of age.

Dr Lindesmith, the National Registry Data report 125 children who are cardiac patients treated with ECMO with a 45% survival rate. In defining criteria for neonatal respiratory failure, we would like to exclude hypoxia due to cardiac disease because in many cases the cardiac disease should be treated *not* by starting ECMO therapy.

If the algorithm is that a diagnosis of cardiac disease is made and we can use ECMO therapy as a bridge to treat with operation, either palliative or definitive, then that certainly makes very good sense.

Dr Johnson, reports several years ago showed up to a 50% incidence of intracranial hemorrhage while on ECMO. The national figure is now down to 16%. We tend to do two things: we tend to try to control our ACTs very carefully; and our experience is that we can keep an ACT within 20 seconds of our desired goal 81% of the time. We only had an ACT over 300 seconds 1.3% of the total 1800 hours on bypass.

We also control blood pressure, keeping the systolic pressure less than 90 mm Hg. This is an important factor in avoiding intracranial hemorrhage, especially in the first 48 hours on ECMO, when we think that the capillary membrane in the brain is at its greatest risk for instability.

Regarding the diaphragmatic hernia and pre-ECMO treatment, 50% of these infants will do well with the operative treatment for diaphragmatic hernia alone. If we take all the infants who have a diaphragmatic hernia and who develop respiratory failure and then place them on ECMO, then we are going to have some downside risk of the treatment with ECMO. Since they underwent hernia repair first, not all of them would require ECMO; then we may be committed to operating on many of them receiving ECMO.

Our feeling is that we should have the children transferred and evaluated in the neonatal intensive care unit. The tendency before was to rapidly transfer the neonates from the ambulance to the operating room, and I think Bohn's study from The Hospital for Sick Children in Toronto, Ontario, showed that a number of these patients can be handled well with a resuscitation for several hours to improve their status metabolically and hemodynamically and then go to the operating room. That is our approach to these infants.

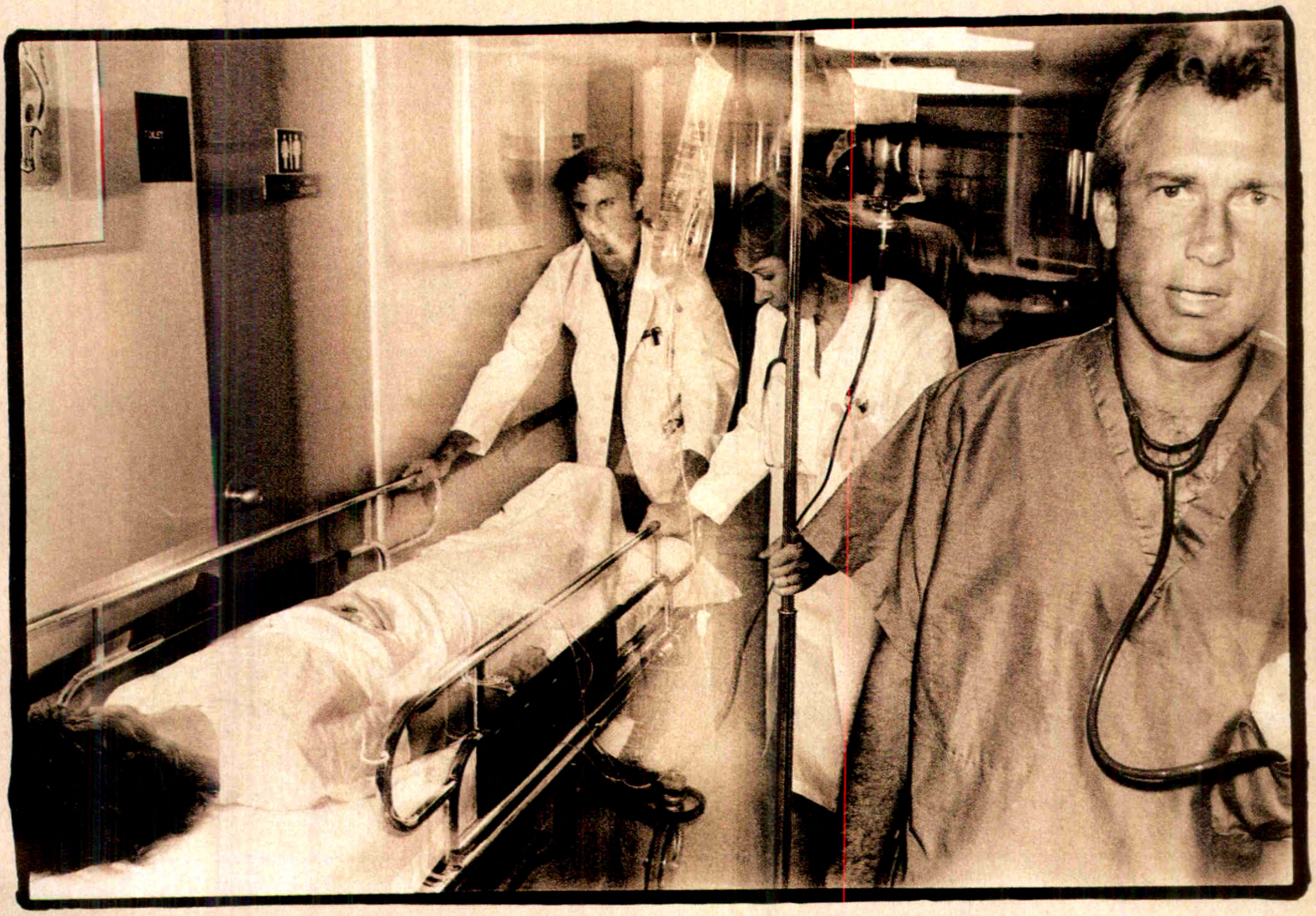
The neonates who have had a diaphragmatic hernia whom we have seen in our nursery have all done well with operative management and have not required ECMO.

Dr Benfield, Pearl O'Rourke, MD, and her colleagues at Boston (Mass) Children's Hospital 3 months ago reported their experience in a prospective randomized trial. They found that the survival rate among neonates treated with conventional maximal therapy was 60%. In comparable infants treated with ECMO, there was a 97% survival rate; therefore, I think there is some excellent recent data in regard to the issue of controls.

Dr Lewis, there are some differences between newborns and adults. Looking critically at the National Institutes of Health collaborative study, the patients that were treated with ECMO did very well. They could not be weaned off, and the problem was that they had been on a ventilator on maximal settings in many cases for an average of 10 days before ECMO was used. Essentially, there was irreversible lung damage. Neonates are different. Neonates have a pop-off valve and a ductus or patent foramen ovale through which they can shunt blood. Most programs have chosen to limit neonates receiving ECMO therapy to those who have been on the ventilator for no more than 7 days as a relative contraindication or an absolute contraindication would be more than 10 days of ventilation management.

The infant also has the ability to further increase lung growth because alveolar growth will continue until the child is 2 years of age. This also answers the question in regard to the physiology of pulmonary function in these infants.

The idea of using PEEP certainly was not something that we thought of. Ted Kolobow, who invented the membrane lung that many centers use in the United States, is affiliated with the National Institutes of Health and has been an advocate of high PEEP for a number of years. Marty Keszler and his colleagues at Georgetown University, Washington, DC, at the AATS meeting reported their results with 50 newborns treated with high PEEP levels and they found that those infants came off bypass after an average of 86 hours of ECMO therapy compared with a national average of 125 hours in comparable patients.



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1. Data available on request from Roerig. **2.** Aldridge KE, Sanders CV, Marier RL: Variation in the potentiation of β-lactam antibiotic activity by clavulanic acid and sulbactam against multiply antibiotic-resistant bacteria. *J Antimicrob Chemother* 1986;17:463-469. **3.** Crombleholme WR, Ohm-Smith M, Robbie MO, et al: Ampicillin/sulbactam versus metronidazole-gentamicin in the treatment of soft tissue pelvic infections. *Am J Obstet Gynecol* 1987;156(Feb):507-512. **4.** Cucharal G, Snydman D, Jacobus N, et al: Comparison of new antimicrobial agents against the *Bacteroides fragilis* group. Abstract, presented at the Annual Meeting of the American Society of Microbiology, Miami Beach, Fla; May 1988. **5.** D'Amato RF, Hochstein L, Pavia M: *In vitro* susceptibilities of aerobic and anaerobic clinical isolates to ampicillin/sulbactam. Presented as a Scientific Exhibit at the 87th Annual Meeting of the American Society of Microbiology, Atlanta, March 1987. **6.** Finegold SM: Anaerobic bacteria: Their role in infection and their management. *Postgrad Med* 1987;81(8):141-147. **7.** Jenkins SG: Susceptibility patterns of *Bacteroides fragilis* group isolates to ampicillin/sulbactam and other selected antibiotics. Presented at a symposium entitled *Ampicillin/Sulbactam: New Strategy for the Treatment of Infectious Disease*. Montreux, Switzerland, July 16-17, 1987, pp 19-20. **8.** Tally FP, Jacobus NV: Activity of sulbactam against recent isolates of aerobic and anaerobic bacteria, abstract 36. Presented at the 23rd International Congress of Antimicrobial Agents and Chemotherapy, Las Vegas, Oct 24-26, 1983 (abs). **9.** Wasilauskas B: Susceptibility of anaerobes to ampicillin-sulbactam and 6 other antimicrobial agents, abstract. Presented at the Annual Meeting of the American Society for Microbiology, Miami Beach, Fla; May 8-13, 1988. **10.** Wexler HM, Harris B, Carter WT, et al: In vitro efficacy of sulbactam combined with ampicillin against anaerobic bacteria. *Antimicrob Agents Chemother* 1985;27:876-878. **11.** Ampicillin/sulbactam (Unasyn). *Med Lett Drugs Ther* 1987;29(August 28):79-81. **12.** Hemsell DL, Wendel GD, Hemsell PG: Combating beta-lactamase enzyme—principal defense mechanism of many pelvic infection pathogens. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **13.** Senft H-H, Stiglmayer R, Eibach HW, et al: Sulbactam/ampicillin versus cefoxitin in the treatment of obstetric and gynaecological infections. *Drugs* 1986;31(suppl 2):18-21. **14.** Newton ER, Gibbs RS: Treatment of postpartum endometritis: A comparison of ampicillin/sulbactam vs. gentamicin plus clindamycin. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **15.** Gunning J: A comparison of parenteral sulbactam/ampicillin versus clindamycin/gentamicin in the treatment of pelvic inflammatory disease. *Drugs* 1986;31(suppl 2):14-17. **16.** Stromberg BV, Reines HD, Hunt P: Comparative clinical study of sulbactam and ampicillin and clindamycin and tobramycin in infections of soft tissues. *Surg Gyn Obstet* 1986;162:575-578. **17.** Kager L, Malmborg AS, Nord CE, et al: A randomized controlled trial of ampicillin plus sulbactam vs. gentamicin plus clindamycin in the treatment of intraabdominal infections: A preliminary report. *Rev Infect Dis* 1986;8(suppl 5):S583-S588. **18.** Bruhat MA, Pouly JL, Le Boedec G, et al: Treatment of acute salpingitis with sulbactam/ampicillin: Comparison with cefoxitin. *Drugs* 1986;31(suppl 2):7-10. **19.** Faro S: Experience with ampicillin/sulbactam for OB/GYN infections. Presented at a symposium entitled *β-Lactamase Inhibitors: Progress with Ampicillin/Sulbactam*. Atlanta, December 6, 1987, p 14 (abs).

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Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*

Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS

UNASYN is generally well tolerated. The following adverse reactions have been reported.

Local Adverse Reactions

Pain at IM injection site—16% Pain at IV injection site—3%
Thrombophlebitis—3%

Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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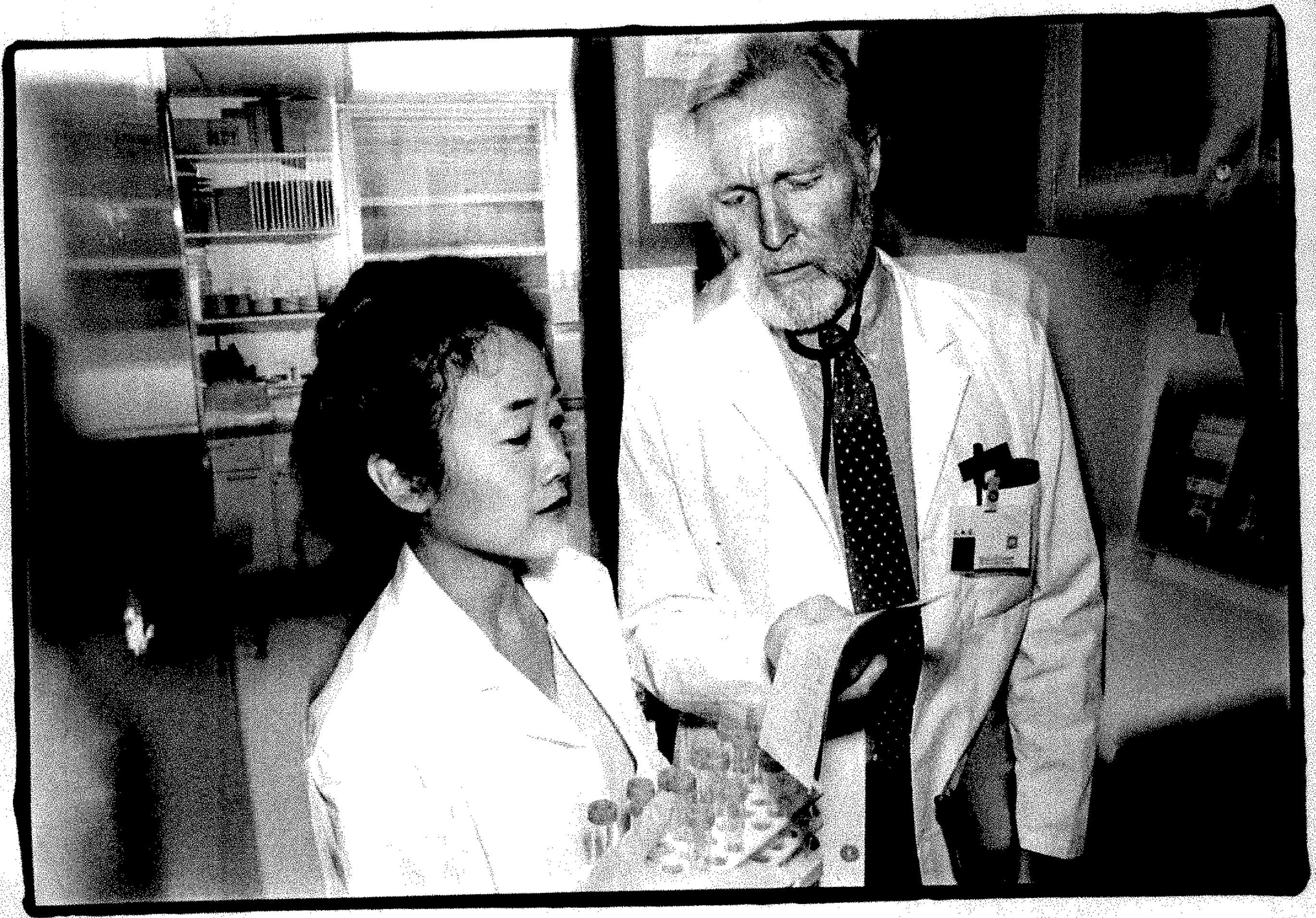

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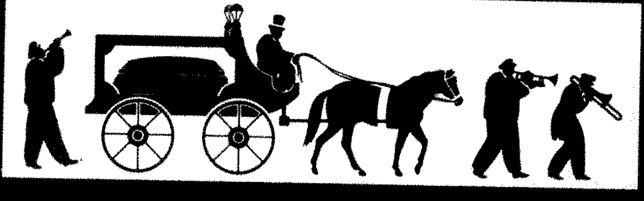

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The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED

PRECAUTIONS

General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN

Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Testape®) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman

Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12

ADVERSE REACTIONS

UNASYN is generally well tolerated. The following adverse reactions have been reported

Local Adverse Reactions

Pain at IM injection site—16%
Pain at IV injection site—3%
Thrombophlebitis—3%

Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients

Additional systemic reactions reported in less than 1% of the patients were itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were

Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH

Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets

Blood Chemistry: Decreased serum albumin and total proteins

Renal: Increased BUN and creatinine

Urinalysis: Presence of RBC's and hyaline casts in urine

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN

Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis

Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena

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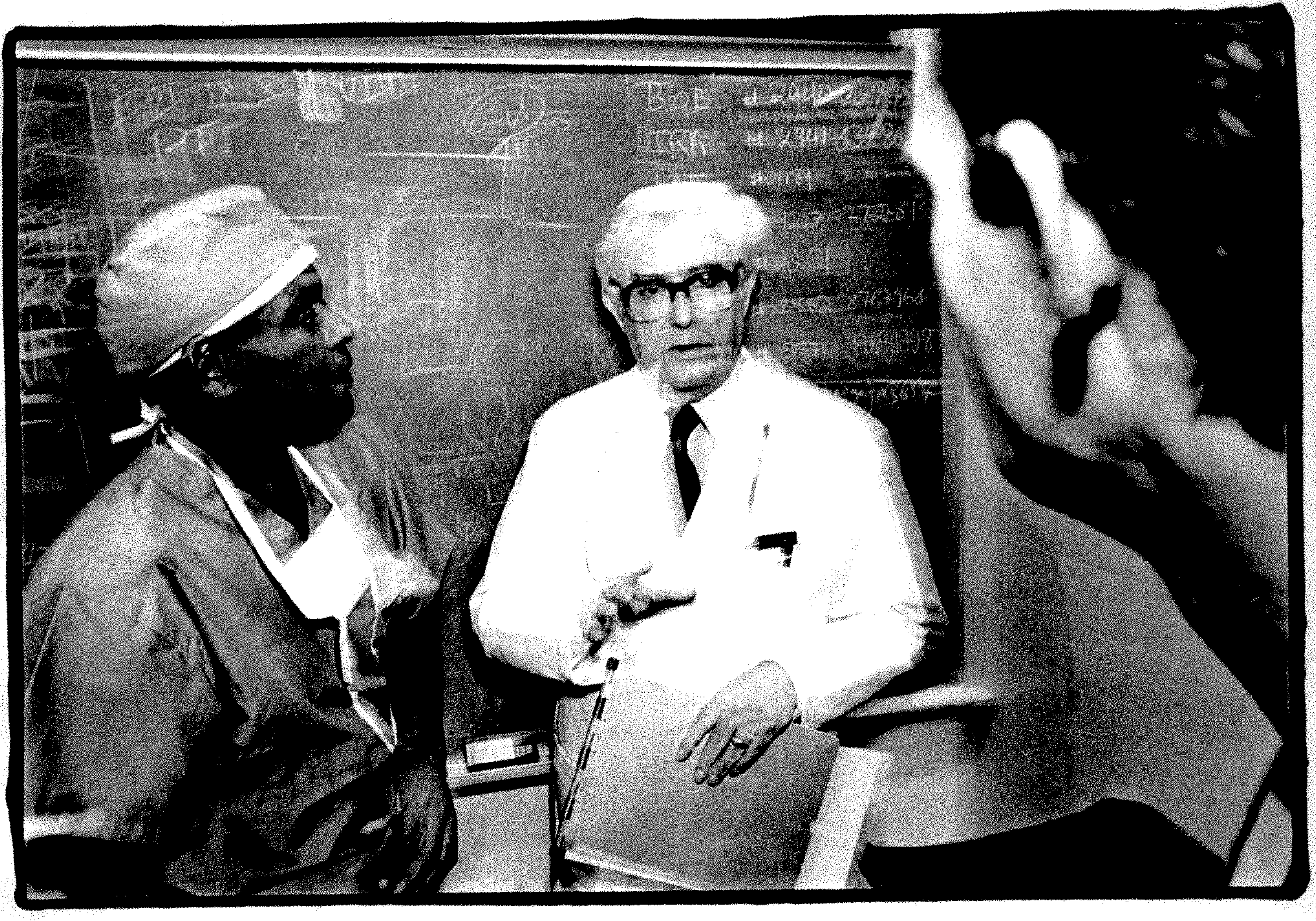

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The Impact of Microinvasion on Axillary Node Metastases and Survival in Patients With Intraductal Breast Cancer

Jan H. Wong, MD; Kelly H. Kopald, MD; Donald L. Morton, MD

• A rational approach to the local treatment of intraductal breast cancer continues to generate considerable debate. However, the finding of an invasive component in intraductal breast cancer is widely regarded as an appropriate indication for axillary node dissection as part of the local treatment and staging of this disease. Despite this view, the natural history of patients with intraductal breast cancer with foci of microinvasion is poorly defined. Between 1965 and 1988, 41 patients with this pathologic finding of intraductal carcinoma with foci of microinvasion were seen at the UCLA Medical Center. Twenty-three patients presented with mammographic abnormalities, while 17 patients presented with a palpable mass. One patient presented with Paget's disease of the nipple. Thirty-three patients underwent axillary node dissection as part of their local treatment. No lymph node metastases were identified. The median follow-up in 37 patients was 47 months. There have been no local recurrences and no deaths from recurrent breast cancer. Intraductal breast cancer associated with microinvasion appears to be an extremely favorable lesion with minimal risk of nodal metastases.

(*Arch Surg.* 1990;125:1298-1302)

An increasing understanding of the natural history and biology of human breast cancer has led to significant advances in the local-regional therapy of this disease. Breast-conserving surgery and radiation therapy have proven to be valid alternatives to mastectomy in most patients with invasive ductal breast cancer.[1,2] However, considerable debate is still generated when clinicians are faced with defining a treatment philosophy for the spectrum of breast cancer in which the natural history and biology of the disease process is less clearly defined. Such is the case for intraductal carcinoma of the breast for which the treatment can range from complete excision alone[3,4] to modified radical mastectomy.[3,5-7] However, it would not be unreasonable to anticipate that the presence of microinvasion in patients with intraductal breast cancer would lead to a biologic behavior similar to infiltrating breast cancer and therefore, would justify similar treatment recommendations. Little information exists concerning the natural history of the pathologic entity of intraductal breast cancer with foci of microinvasion to support or negate this view.

Data are lacking because intraductal breast cancer with microinvasion has generally been categorized with a spectrum of pathologic entities that includes intraductal breast cancer and infiltrating breast cancer less than 0.5 cm in diameter. This group of diseases has most commonly been referred to as "minimal breast cancer."[8] Minimal breast cancer has been associated with a relatively good prognosis with a reported overall axillary node metastases rate of approximately 5%.[9] However, the incidence of nodal metastases in patients with minimal breast cancer with invasion into the surrounding stroma has been reported to be as high as 31.5%.[10] It is apparent that these histologic findings may represent a spectrum of disease entities with different biologic behavior and a unique natural history.

A survey conducted by the American College of Surgeons[11] identified approximately 10% of female breast cancers to be either in situ (1.9%) or minimally invasive carcinomas (8.4%). With the increasing use of screening mammography, a concomitant increase is anticipated in the frequency with which these lesions will be diagnosed. To better define the natural history of intraductal breast cancer with microinvasion, we examined the presentation, treatment, and clinical course of patients with the pathologic diagnosis of intraductal breast cancer with microinvasion treated at the UCLA Medical Center. Our results suggest that patients with this pathologic entity are at low risk for axillary node metastases and can anticipate an excellent survival.

PATIENTS AND METHODS

From 1967 through 1988, 2244 patients with carcinoma of the breast (intraductal, lobular carcinoma in situ, infiltrating ductal car-

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Read before the 61st Annual Meeting of the Pacific Coast Surgical Association, Laguna Niguel, Calif, February 19, 1990.

Reprint requests to Department of Surgery, UCLA School of Medicine, 9th Floor Factor Bldg, Los Angeles, CA 90024 (Dr Wong).

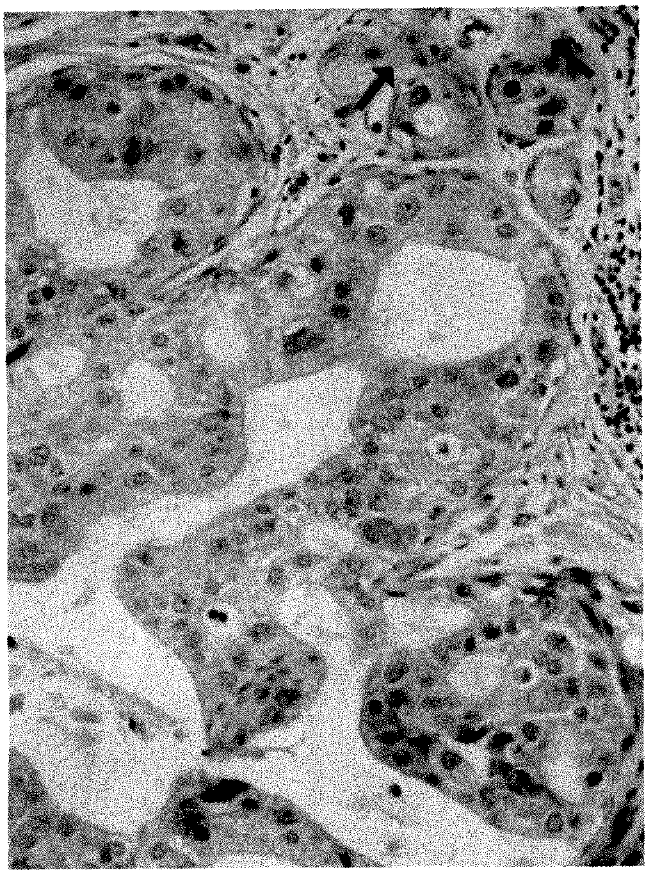

Fig 1.—Photomicrograph of intraductal breast cancer with foci of microinvasion. This figure represents largely an intraductal component of breast cancer with only a microscopic finding of a few tumor cells invading beyond the basement membrane of two ducts (arrows) (hematoxylin-eosin, original magnification × 100).

cinoma and infiltrating lobular carcinoma) were admitted to the UCLA Medical Center. The final pathologic diagnoses of these 2244 patients were individually reviewed along with a computerized search of the UCLA Medical Center Department of Pathology database. We identified 177 patients (8%) whose final pathologic diagnosis was intraductal breast cancer. An individual review of each of the pathologic records of these 177 patients revealed 41 patients with foci of microinvasion in addition to intraductal breast cancer. These patients form the basis of this analysis. These 41 patients need to be distinguished from the substantially larger populations of patients with infiltrating breast cancer in whom carcinoma cells are readily identified in the surrounding stroma.

Patients in whom the lesion was identified by mammography underwent localization prior to biopsy. A standard technique was used in which the mammographic abnormality was identified and localized both by needle and with the injection of methylene blue dye. Following excision, presence of the abnormality was confirmed with standard specimen mammography. An excisional biopsy was performed when a palpable mass was present.

The definition of microinvasion ranges from a few cells penetrating the basement membrane to include tumors in which up to 10% of the specimen contains an invasive component.[12] The diagnosis of intraductal breast cancer with microinvasion, in this report, was based on the findings of breast cancer cells confined to the duct system of the breast with only a microscopic focus of malignant cells invading beyond the basement membrane of the duct as determined by light microscopy (Fig 1), and was made only after extensive sectioning of the specimen. This pathologic diagnosis needs to be distinguished from the term *minimally invasive microinvasion*, which has commonly been applied to invasive breast cancer less than 1 cm in diameter.[13,14] It should be emphasized that patients in whom the biopsy diagnosis revealed intraductal breast cancer with microinvasion but who, on complete removal of the lesions, had more extensive, infiltrating breast cancer, and patients with infiltrating breast cancer and areas of microinvasion, were excluded from this analysis, as were patients with the diagnosis of lobular carcinoma in situ with foci of microinvasion.

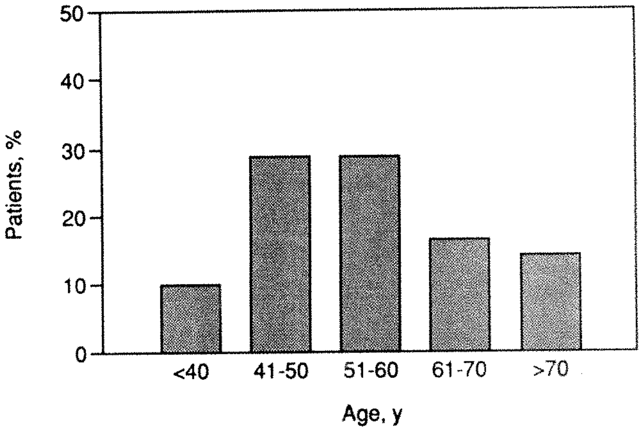

Fig 2.—Age distribution of patients with intraductal breast cancer with foci of microinvasion. The mean age of patients was 54 years.

RESULTS

Patients

Forty-one patients with intraductal breast cancer and microinvasion were identified. These 41 patients represent fewer than 2% of all patients admitted to the UCLA Medical Center with the diagnosis of carcinoma of the breast during the study period. The patients were all women and ranged in age from 25 to 89 years (mean, 54 years) (Fig 2).

Presentation

The increasing use of screening mammography[15] has resulted in an increasing diagnosis of "early" breast cancer. As shown below, more than half of the patients diagnosed with intraductal carcinoma with microinvasion presented with mammographic abnormalities alone that prompted biopsy:

Presentation	No. of Patients
Mammographic abnormality	
Microcalcifications	18
Nonpalpable mass	5
Palpable mass	17
Paget's disease	1

Microcalcifications were the most common abnormalities. One patient presented with Paget's disease of the nipple. The remaining 17 patients had palpable masses. The majority of these conditions were diagnosed prior to 1980. The palpable masses ranged from 1 to 4 cm (mean, 1.6 cm) in diameter.

Treatment

Twenty-six patients underwent some form of mastectomy, as indicated below:

Treatment	No. of Patients
Modified radical mastectomy	22
Simple mastectomy	2
Radical mastectomy	2
Breast-conserving surgery and radiation therapy	9
Local excision	1
Whole breast irradiation	1

Modified radical mastectomy was the most common procedure. However, two patients underwent radical mastectomy and two underwent simple mastectomy alone. Nine patients underwent breast-conserving surgery, axillary node dissection, and postoperative radiation therapy. One patient underwent local excision alone, and another underwent whole breast irradiation alone. The use of mastectomy in the treatment of intraductal breast cancer with microinvasion was as common before the increase in data supporting the efficacy of breast-conserving treatment for invasive breast cancer[1,2] as after. Half the mastectomies were performed after the National Surgical Adjuvant Project for Breast and Bowel Cancer protocol B-06 results were published.[2] In contrast, the majority of patients undergoing breast-conserving surgery and radiation therapy did so after this report was published.

Outcome

The mean number of lymph nodes removed at the time of axillary node dissection was 25 (range, seven to 54), reflecting to some degree the extent of the axillary node dissection performed. No regional node involvement was identified in the 33 patients who underwent axillary lymph node dissection. Four patients were unavailable for follow-up. The median follow-up of the remaining 37 patients has been 47 months (range, 18 to 216 months). There have been no clinical axillary recurrences in patients who did not undergo axillary node dissection. Additionally, there have been no local recurrences in this group of patients. One patient died 10 years after treatment for her intraductal breast cancer with microinvasion without evidence of recurrent breast cancer. No other patient died of recurrent breast cancer.

COMMENT

This report describes the outcome of patients with intraductal carcinoma who, on light microscopy, have a component of microinvasion. The results show that intraductal breast cancer with microinvasion has not been associated with nodal metastases in our experience and is associated with an extremely favorable prognosis. It should be emphasized that intraductal breast cancer with foci of microinvasion is distinctly different from those breast cancers classified as *minimally invasive breast cancer*, a term that has commonly been used to characterize invasive breast cancers smaller than 1 cm in diameter.[13,14] Our report does not attempt to address the question of accurately identifying this pathologic entity or the potential sampling error when performing a biopsy of either palpable or mammographic abnormalities. Because there were no deaths from breast cancer and no local recurrences, no benefit can be attributed to any of the modalities employed in treating this disease entity.

The pathologic diagnosis of intraductal breast cancer with foci of microinvasion is based on the light microscopic evidence of cancer cells beyond the basement membrane of the normal duct. The pathologic criteria for intraductal breast cancer with microinvasion and the guidelines for diagnosis are far from precise. Some have applied the term *microinvasive breast cancer* to describe invasive tumors smaller than 0.5 cm in diameter,[8] others to describe tumors smaller than 1.0 cm in diameter,[13,14,16] and still others to describe certain histologic types of infiltrating cancer such as medullary, colloid, and tubular carcinomas.[17] Although the diagnosis is subject to the interpretation of the pathologist, it is apparent that following extensive section of the specimen, a general consensus of this entity exists among our pathologists at UCLA.

The incidence of intraductal breast cancer with microinvasion is difficult to determine, largely because it has been grouped together with a number of pathologic entities under the term *minimal breast cancer* and to our knowledge, few institutions have had the opportunity to treat substantial numbers of these patients.[18-22] Our experience indicates that intraductal breast cancer with microinvasion is a relatively uncommon finding, representing approximately 2% of all breast cancer admitted to the UCLA Medical Center. Perhaps for this reason, the natural history of this entity has been poorly defined and has been assumed to have a biologic behavior similar to the usual infiltrating breast cancer. Mammography remains the most sensitive technique for the detection of early breast cancer.[23] With evidence that detection of early breast cancer can influence outcome,[24] it is anticipated that with the increasing use of screening mammography the incidence of mammographically identified breast cancers will increase

Patients with intraductal breast cancer and microinvasion may present with either a palpable mass or mammographic abnormalities. Increasing tumor size has repeatedly been demonstrated to be associated with a poorer prognosis as well as the presence or absence of nodal metastases.[15,25] However, a palpable mass seemed not to have an adverse impact on outcome in this series of patients, suggesting that the histologic characteristics of the tumor as intraductal breast cancer with only a focus of microinvasion is a more important prognostic feature than tumor size.

The incidence of lymph node involvement in patients with intraductal breast cancer with microinvasion is unknown. It has been suggested to be up to 5% in the spectrum of disease included under the term *minimal breast cancer*, as high as 5% in intraductal cancer alone,[9] and up to 31.5%[10] when "microinvasion" is present. This later group may, in fact, include invasive breast cancer less than 1 cm in diameter. However, increasing reports indicate that the incidence of lymph node involvement is substantially less. In our experience, lymph node involvement is uncommon in patients with intraductal breast cancer with foci of microinvasion.

Determining the optimal local treatment for intraductal breast cancer with microinvasion from our data is not possible, since we have not experienced any treatment failures during the follow-up periods. Patients in this series underwent a variety of surgical procedures, with the addition of radiation therapy in certain instances without local recurrence. The value of mastectomy in the local control of breast cancer and in intraductal breast cancer, in particular, has been well documented. Interestingly, a treatment philosophy for patients with intraductal breast cancer alone remains controversial although mastectomy is commonly recommended as the prudent decision.[7] However, the presence of microinvasion seems to justify conservative breast surgery, axillary node dissection, and radiation therapy as an alternative treatment. The demonstrated efficacy of mastectomy in the treatment of intraductal breast cancer seems to be directly applicable to intraductal breast cancer with microinvasion, as are the results of prospective randomized trials comparing mastectomy and breast conserving surgery and radiotherapy.[1,2] Our results suggest that the routine inclusion of lymph node dissection in the management of intraductal breast cancer with microinvasion is not necessary. Because of the potential sampling error when performing a biopsy, however, a reasonable approach to this entity might be to perform a complete excision of the tumor. If the final pathologic evaluation of all tissue identifies an infiltrating carcinoma, an axillary node dissection can subsequently be performed to evaluate what cancer stage the patient is in. It is apparent that evaluation of current treatment, both local and systemic, is best done in the setting of a clinical trial.

Adjuvant chemotherapy has become an important component in the treatment of breast cancer.[26] Attempts are now being made to duplicate the benefits achieved with adjuvant chemotherapy in patients with nodal metastases in patients with node-negative breast cancer. This, however, remains an area of continued controversy. It is apparent that in a disease entity in which the natural history remains poorly defined, there is no role for evaluating the impact of adjuvant chemotherapy outside of a clinical trial. In fact, our results suggest that the finding of foci of microinvasion in patients with intraductal breast cancer is not ominous and the natural history of this histologic entity is more similar to intraductal breast cancer alone than invasive breast cancer. However, since the natural history of recurrent breast cancer extends well beyond the median follow-up of our report, continued long-term follow-up will be necessary to confirm our initial observations. These results, however, suggest that patients with intraductal breast cancer with microinvasion probably should be distinguished from those with invasive breast cancer when examining outcome following adjuvant chemotherapy. A better understanding of the natural history and biology of breast cancer will ultimately lead to optimal treatment recommendations.

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Discussion

R. MARK VETTO, MD, Portland, Ore: Not so long ago, derision greeted surgeons who suggested that a lumpectomy might be used to treat breast cancer. Perhaps this attempt to eliminate axillary dissection in a specific class of breast cancer is the next step.

However, the earlier tumors that we see today and the increasing ways in which we categorize them in terms of size, invasion, type, endocrine markers, flow cytometry, and extent of regional metastases if any, have made the surgical management decisions much more difficult. Intraductal carcinoma without invasion is multifocal in 50% of the cases and will eventually recur as cancer in the same breast in 30% to 50% of the cases. Intraductal cancer does not require axillary dissection, but nevertheless exhibits axillary metastases in 1% to 5% of patients. In our institution, intraductal carcinoma is commonly treated with local resection and radiation, and many of these patients qualify for the National Surgical Adjuvant Project for Breast and Bowel Cancer B-17 protocol. However, some of our patients undergo local resection alone, or total mastectomy, or occasionally modified radical mastectomy.

At the other extreme, minimally invasive ductal cancers, usually detected by screening mammography, when not treated with modified radical resection are treated with local excision, staging axillary dissection, and breast radiation. The authors state that the incidence of axillary metastases in this group of patients is 5%, although others have reported a higher incidence.

The authors propose to establish a new category of patients with ductal carcinoma in whom the tumor is not intraductal and minimally invasive, but is microinvasive and has not exhibited axillary metastases in the 37 cases presented. This is indeed a noble effort to eliminate axillary dissection, but there are several criticisms.

Microinvasion is difficult to unequivocally establish and is subject to sampling error. Even intraductal in situ tumors have an incidence of axillary metastasis that may be related to missing an invasive area when cutting the specimen. Four of the 41 patients described were unavailable for follow-up, which represents a possible undiscovered recurrence rate of 10%. There is some question about the length of follow-up despite the median of 47 months, since nearly two thirds of the patients had a nonpalpable tumor that required localization and therefore must have been of a more recent origin. In fact, one of the patients was followed up for 18 months.

On the positive side, if the incidence of axillary metastases with small ductal carcinomas is 5% or even 10%, for every 100 axillary dissections we do, 90 or 95 are not necessary. We certainly ought to try to do better than that.

So the real question in my mind is whether we should continue to indiscriminately perform staging axillary dissection for small ductal cancers when physical examination of the axilla yields no results and other risk factors are absent. Dr Wong, I am very attracted to the notion that we ought to inch up to where we do not perform so many "negative axillary dissections," and perhaps the identification of the microinvasive ductal tumor is the first inch. Certainly, it can be no greater than an inch since tumors with the degree of invasion you describe represent only 2% of the breast pool at your institution.

BALAZS I. BODAI, MD, Carmichael, Calif: At Kaiser Permanente in Sacramento (Calif), we treat upwards of 400 breast cancers per year. We are currently doing about 25 000 screening mammograms annually, soon to reach 35 000.

I see these patients, probably approximately one every other month. I do not know what my colleagues are seeing, but I have certainly been excited by this study to review our experience.

Despite the fact that the recurrence rate is as low as it is, do you still offer all the options to the patient for the treatment of breast cancer? That is, from doing nothing, ie, observation, to performing a modified radical mastectomy, and where do you feel that their best choice would lie? Would your recommendations be tempered at all by the patient's age, that is, would you recommend it for a 30-year-old woman as opposed to a 60-year-old woman?

RICHARD P. SAIK, MD, La Jolla, Calif: The authors have a unique sampling of 22 women who underwent mastectomy for minimal cancer. I wonder if they reviewed the pathologic specimens to see if there were other foci of cancer or microinvasion in other areas of the breast.

ARMANDO E. GIULIANO, MD, Los Angeles, Calif: Microinvasive cancer is invasive. The presentation would lead us to believe that intraductal and microinvasive are the same. Microinvasive cancer has shown that it has the ability to penetrate the basement membrane and metastasize. Along the spectrum of breast cancers, we know that the smaller the cancer, the less likely it is to have positive nodes. It is safe to assume that these are early lesions with a low incidence of positive nodes, but we should perform an axillary dissection.

A negative axillary dissection is not an unnecessary procedure. It tells you whether there are lymph node metastases or not. It is not therapeutic, but then again, the removal of microscopically positive nodes may not be therapeutic. Are you really advocating that if a woman comes in with a palpable mass (as 17 of your patients did) and she has microinvasion, we do not perform an axillary dissection?

CLARE G. PETERSON, MD, Portland, Ore: Invasive cancer is invasive cancer. I have spent my life in surgery regretting the lost opportunities to contain small malignancies by adequate en bloc operations. There should not be much confusion about the fact that microinvasion of breast cancer with breakthrough of the basement membrane is truly invasive infiltrating carcinoma of the breast with all the metastatic capabilities of such a lesion.

The message of this report, demonstrating microinvasion (small, early, invasive cancers) treated by en bloc procedures (total mastectomy or modified radical mastectomy), shows excellent survival results free of cancer at this time.

This is vindication of the en bloc principle in the treatment of invasive breast cancer—the clinical arguments and dilemmas remaining being related to the true staging of the cancer before operation, and the extent and completeness of the en bloc resectional procedure carried out. I cannot agree with the categorical and contradictory statement that, "in this setting," axillary node dissection is unwarranted.

DR MORTON: Our data clearly indicate that axillary lymph node metastases and recurrence are very rare in women who have microinvasive intraductal carcinoma. Thus, if one can unequivocally make such a diagnosis, axillary node dissection does not appear to be indicated. We agree that this conclusion must be regarded as preliminary until more data are accumulated. We cannot be dogmatic when the total number of such patients is only 41. None of these patients had either lymph node metastases or recurrence after a 47-month median observation period, and it is unlikely that larger numbers or longer follow-up will change this conclusion. Nevertheless, we challenge you to review your own experience with this entity and prove us wrong.

One important question that our study does not answer nor attempt to answer relates to the multifocal nature of breast intraductal carcinoma and the frequency with which the initial biopsy results will be interpreted as microinvasive intraductal carcinoma, and, after subsequent mastectomy, other areas of frankly invasive intraductal carcinoma will be found with examination of the entire breast. Such patients would not have been included in our review because we were searching for cases of intraductal carcinoma with microinvasion only. Therefore, we must know how frequently pathologic examination of the entire mastectomy specimen leads to a modification of the initial diagnosis.

Recurrence time is inversely proportional to the size of the lesion. That is, a smaller lesion may take longer to recur than a larger one. We need data from more centers and a longer follow-up before changing our routine treatment from a properly conducted procedure that treats the entire breast by mastectomy or a small procedure in which the entire breast is treated by radiation. This study never implies that the whole breast should not be treated. It only indicates that the patients with intraductal breast cancer and microinvasion have an excellent prognosis and a low incidence of axillary node metastases; all patients in this group except for one had treatment of the entire breast. Since we had up to 20 years of follow-up in some of our cases, I doubt if longer follow-up will change the basic conclusion.

Dr Bodai, we do discuss all options for therapy with the patients and advise mastectomy or local resection and radiation. Age cannot be a primary consideration in terms of such discussions; the elderly woman is often as anxious to have breast preservation as a young woman.

Dr Saik, we did not get out the 177 cases and go through the breast by serial sections to look for additional areas of microinvasion. We would not have included those cases in our review in which additional areas of frankly invasive carcinoma were found by the pathologists in the mastectomy specimens.

Dr Peterson, it is important to point out that when no treatment failures occur, no benefit can be attributed to any treatment modality. It does not support the en bloc principle, but rather, if anything, suggests the equivalent efficacy of "lesser procedures" in this pathologic entity.

Dr Giuliano, one has to either take the position that one will routinely perform an axillary dissection on every case such as this, or be committed to go back and do an axillary dissection if, on pathologic examination of the entire specimen, other areas of frank invasion are found. Until we know how frequently the diagnosis will be changed by examination of the entire specimen, it may be inappropriate to perform an axillary dissection at the initial operation when this information may change the treatment plan.

Immediate Breast Reconstruction Following Mastectomy Is as Safe as Mastectomy Alone

Adele L. Vinton, MD; L. William Traverso, MD; R. David Zehring, MD

• We evaluated wound complications and potential risk factors after mastectomy with immediate breast reconstruction and compared them with similar data after modified radical mastectomy. The incidences of infection, seroma, hematoma, and epidermolysis were compared among 395 patients (305 with modified radical mastectomies and 90 with mastectomy with immediate breast reconstruction) from Virginia Mason Medical Center, Seattle, Wash, between 1983 and 1989. Obesity, age (60 years or older), smoking, antibiotics, and wound drainage were examined as possible risk factors. There were more wound complications in the modified radical mastectomy group (48% vs 31%), and specifically, more seromas (30% vs 13%). In the modified radical mastectomy group, age of 60 years or older was associated with seroma and infection, drainage greater than 30 mL per day (at time of drain removal) with seroma, and smoking with epidermolysis. In the mastectomy with immediate breast reconstruction group, obesity was associated with seroma and epidermolysis. We conclude that mastectomy with immediate breast reconstruction appears to be as safe as modified radical mastectomy alone with respect to wound complications.

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Mastectomy with immediate breast reconstruction (MIBR) has become an accepted procedure in the treatment of breast carcinoma. There have been several recent studies addressing the concerns related to immediate breast reconstruction, including the potential for compromise of cancer cure and the issue of postoperative wound complications. All have concluded that MIBR is a safe and acceptable procedure in the treatment of breast cancer.[1-4]

However, to our knowledge, no study has compared in detail the incidence of wound complications after MIBR with those after modified radical mastectomy (MRM) alone, or addressed the possible risk factors for wound complications. This study examines the incidence of wound complications for both procedures, and illustrates the safety of MIBR when compared with MRM alone. It also defines certain factors that increase the incidence of wound complications following each procedure.

MATERIALS AND METHODS

We reviewed the charts of 305 women undergoing MRM and 90 women undergoing MIBR with submuscular breast implants for breast cancer at Virginia Mason Medical Center, Seattle, Wash, between January 1, 1983, and November 30, 1989. The following data were collected: age, sex, height, weight, stage of cancer, smoking history, type of operation, date of surgery, use of prophylactic antibiotics, volume of closed suction wound drainage, and complications (infection, hematoma, seroma, or epidermolysis).

The incidences of infection, hematoma, seroma, and epidermolysis were determined for each group (MRM and MIBR) and complication rates for the two operations were compared. The incidence of each type of complication for subsets of cases with suspected risk factors for complications (obesity, smoking, and age 60 years or older) was determined. Then the complication rates of these patients at risk were compared with the rates in patients not at risk. The use of intravenous antibiotics immediately preoperatively was examined for association with wound infection, and the amount of drainage during the 24 hours prior to removal of the last drain was analyzed with respect to seroma rate. Variables were analyzed using the χ^2 test, Fisher's Exact Test, and Student's *t* test, where appropriate. Differences were considered significant at $P<.05$.

For the purpose of this study, obesity was defined as body mass index ([weight in kilograms]/[height in meters^2]) equal to 27.3 or greater.[5] Patients were grouped in the category of "smoker" if they answered affirmatively to the question "Do you smoke?" asked by the nurse or physician evaluating the patient before surgery. Infection was defined as any wound appearance that prompted treatment with antibiotics, whether or not organisms were cultured. Epidermolysis was defined as any wound described as having some degree of skin necrosis. A seroma was any subcutaneous fluid collection, whether or not aspirated. A hematoma was any fluid collection described as a hematoma, or bloody (not serosanguineous) fluid obtained at the time of aspiration.

RESULTS

Modified radical mastectomies (n = 305) were performed by 12 general surgeons at Virginia Mason Medical Center. Im-

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Table 1.—Study Population Preoperative Data*

	MRM (No.)	MIBR (No.)
Mean age, y	61 (305)	49 (90)†
Age ≥60 y	59% (305)	16% (90)†
Obese	35% (260)	25% (72)
Smoker	22% (304)	35% (90)
Antibiotics	46% (305)	80% (90)†

*MRM indicates modified radical mastectomy, and MIBR, mastectomy with immediate breast reconstruction.

†$P<.01$, MRM vs MIBR.

Table 2.—Breast Cancer Staging*

Stage	MRM, % (n=292)	MIBR, % (n=72)
0	4	13†
I	40	42
II	47	37
III	7	7
IV	2	1

*MRM indicates modified radical mastectomy, and MIBR, mastectomy with immediate breast reconstruction.

†$P<.01$, MRM vs MIBR.

mediate breast reconstructions (n=90) were performed by four plastic surgeons; 72 (80%) of the MIBRs included in the study were performed by one plastic surgeon (R.D.Z.). Fifty-seven of these were performed using tissue expanders initially before permanent implants.

Study population preoperative data are shown in Table 1. Height and weight data were available for 260 (85%) of the MRM group and 72 (80%) of the MIBR group. Data regarding smoking history were available for 304 (99.7%) of the MRM group and 89 (99%) of the MIBR group. Age and prophylactic antibiotic use data were available for all patients. In the MIBR group (compared with the MRM group), significantly fewer patients were older than 60, and significantly more received prophylactic antibiotics (cefazolin sodium or cefotetan disodium).

Staging of breast cancer in the two groups is shown in Table 2 (using the TNM System, 1989). Significantly more patients had in situ carcinoma in the MIBR group. Data regarding the use of closed suction drains postoperatively are shown in Table 3. Closed suction drains were placed in all patients. Two drains (one beneath the flap and one in the axilla) were placed in all MRM patients for whom drain data were available (flap drains, n=286; axillary drains, n=277). One drain was placed in the axilla of all patients in the MIBR group for whom axillary drain data were available (n=63). In addition, 12 patients in the MIBR group had flap drains placed. The mean postoperative days on which drains were removed are shown in Table 3. Flap drains were left in place significantly longer in the MIBR group, and axillary drains were left in place significantly longer in the MRM group ($P<.01$ for both). The volume of drainage in the 24 hours prior to removal of the last drain is also shown in Table 2, and was available in 174 of the MRM group and 48 of the MIBR group. There was no difference in mean volume of drainage in the 24 hours prior to removal of the last drain between the two groups. The number of patients with volume of drainage greater than or equal to 30 mL in the 24 hours prior to removal of the last drain in each group was compared, and no significant difference was found.

Table 3.—Closed Suction Drain Data*

	MRM (No.)	MIBR (No.)
Flap drain out (mean PO Day)	7 (286)	10 (12)†
Axillary drain out (mean PO Day)	11 (277)	8 (63)†
Last drain out, mL (mean volume last 24 h)	27 (174)	26 (48)
Volume >30 mL/24 h when drain out, %	24 (174)	17 (48)

*MRM indicates modified radical mastectomy; MIBR, mastectomy with immediate breast reconstruction; and PO, postoperative.

†$P<.01$ MRM vs MIBR.

Table 4.—Wound Complications*

	MRM, %	MIBR, %
Any complication	48	31†
Infection	13	13
Seroma	30	13†
Hematoma	5	2
Epidermolysis	18	16

*MRM indicates modified radical mastectomy, and MIBR, mastectomy with immediate breast reconstruction.

†$P<.01$, MRM vs MIBR.

Data regarding complication rates are shown in Table 4. Overall, there were significantly fewer complications and specifically fewer seromas in the MIBR group. Data regarding risk factors for complications in both groups are shown in Tables 5 through 7.

Table 5 reveals that in the MRM group infections and seromas both occurred significantly more frequently in patients aged 60 years or older, while age was not a significant risk factor for complications in the MIBR group. Obesity was not found to be a risk factor for complications in the MRM group (Table 6); however, it was a significant risk factor for both seroma and epidermolysis in the MIBR group. Table 7 reveals that in the MRM group, smokers experienced epidermolysis more frequently, and in the MIBR group, smoking was not a risk factor for complications.

The use of prophylactic antibiotics was analyzed with respect to infection in both groups. In the MRM group, 16% of patients who received prophylactic antibiotics developed infection as compared with 10% of patients who did not receive antibiotics. In the MIBR group, 14% of patients who received antibiotics developed infections, compared with 12% who did not receive antibiotics. Neither of these differences was statistically significant. To determine whether antibiotic use influenced the incidence of wound infection in specific groups at risk, patients older than 60 years, smokers, and obese patients in the MRM group were analyzed separately. No difference in infection rates was seen in any group whether or not antibiotics were given.

Cultures yielded organisms in 16 patients with infection (40%) in the MRM group, and two patients with infection (17%) in the MIBR group. The difference is not significant. The remainder of infections in the two groups were described as wound erythema only, and may or may not have been true cellulitis. In those patients whose cultures yielded organisms, there was no significant difference in wound infection rates whether or not prophylactic antibiotics were given. The or-

Table 5.—Risk Factor: Age ≥60 y*

	Age ≥60 y		Age <60 y	
Complication	MRM Group	MIBR Group	MRM Group	MIBR Group
No.	179	14	126	76
Infection, %	17	21	8†	12
Seroma, %	36	14	20‡	13
Hematoma, %	6	0	3	3
Epidermolysis, %	18	14	18	16

*MRM indicates modified radical mastectomy, and MIBR, mastectomy with immediate breast reconstruction. No comparisons in the MIBR group were significant.

†$P<.01$.

‡$P<.05$ for age greater than or equal to 60 years compared with age less than 60 years.

Table 6.—Risk Factor: Obesity*

	Obese		Nonobese	
Complication	MRM Group	MIBR Group	MRM Group	MIBR Group
No.	92	31	168	41
Infection, %	18	13	10	17
Seroma, %	28	38	30	10†
Hematoma, %	5	6	3	2
Epidermolysis, %	21	38	14	8†

*MRM indicates modified radical mastectomy, and MIBR, mastectomy with immediate breast reconstruction.

†$P<.05$, obese vs nonobese. No comparisons were significant in the MRM Group.

Table 7.—Risk Factor: Smoking*

	Smoker		Nonsmoker	
Complication	MRM Group	MIBR Group	MRM Group	MIBR Group
No.	67	22	231	67
Infection, %	10	18	14	12
Seroma, %	31	18	30	12
Hematoma, %	6	5	4	2
Epidermolysis, %	49	18	14†	15

*MRM indicates modified radical mastectomy, and MIBR, mastectomy with immediate breast reconstruction.

†$P<.01$, smoker vs nonsmoker. No comparisons were significant in the MIBR Group.

ganisms yielded by cultures in the MRM group included *Staphylococcus aureus* in 11 patients, *Staphylococcus epidermidis* in two patients, enterococcus in one patient, yeast in one, and *Pseudomonas* in one. *Staphylococcus aureus* was the only organism yielded in the two patients in the MIBR group with culture-positive infections.

Volume of wound drainage in the 24 hours before removal of the last drain was analyzed as a risk factor for seroma in both groups. In the MRM group, 49% of patients with drainage volume greater than 30 mL in the 24 hours prior to removal of the last drain developed seromas, compared with 24% in patients whose drains were removed with drainage in the 24 hours prior to removal of the last drain of 30 mL or less. This difference is significant, with $P<.01$. In the MIBR group, no patient with drainage volume greater than 30 mL developed seromas, compared with 10% of patients with drainage volume less than or equal to 30 mL in the 24 hours before drain removal. This difference is not significant.

Complications related specifically to the breast prosthesis occurred in five patients (6%) in the MIBR group. Exposure of the breast prosthesis occurred in one patient, requiring removal of the prosthesis; near exposure occurred in another patient, but prosthesis removal was not necessary. One other prosthesis became dislodged, one deflated, and one removed secondary to excessive pain at the patient's request. This resulted in a prosthesis loss rate of 4%.

COMMENT

To our knowledge, the percentage of patients having any wound complication after MRM has not been previously reported. Other studies have reported the incidence of specific types of wound complications for MRM or combined the complication rates for several types of breast surgery. Therefore, we are unable to compare our overall complication rate in the MRM group of 48% with other studies in the literature. No other study has analyzed in detail the wound complication rates for MRM compared with those for MIBR. One study reported an overall wound complication rate for MIBR. Noone et al[3] found a wound complication rate of 24% in 185 patients undergoing MIBR with either submuscular implants or myocutaneous flaps. This is similar to our finding of an overall complication rate of 31% in the MIBR group.

Feigenberg et al[6] reported wound complications in 100 modified radical and 100 radical mastectomies. Ten percent of MRMs developed seromas, 4% developed infections, and 3% developed skin necrosis. Hayes and Bryan[7] reported 100 Patey mastectomies with an 18% infection rate, 9% epidermolysis rate, and 25% seroma rate. Corneillie et al[8] reported 405 MRMs, 131 tylectomies or segmentectomies with axillary dissection, and 11 simple and 6 radical mastectomies. In the MRM group, infection developed in 1.3%, hematoma in 1.3%, epidermolysis in 2.9%, and seroma in 12.5%. Budd et al[9] studied 19 total mastectomies, 38 modified radical, and 89 radical mastectomies. In the MRM group, there were seromas in 16%, infections in 5%, hematomas in 3%, and skin necrosis in 32%.

Feller et al[1] reported 100 mastectomies with immediate breast reconstruction and found a 2% infection rate and a 2% hematoma rate. Webster et al[4] evaluated 85 patients who underwent MIBR using both implant and flap reconstructions and found a 41% complication rate, a 14% infection rate, a 5% epidermolysis rate, and an 11% incidence of prosthesis loss. Frazier and Noone[2] studied 70 patients undergoing immediate breast reconstruction with submuscular prosthetic implants and found a complication rate of 8% and an infection rate of 4%. Noone et al[3] reported the largest series, with 185 patients (both prosthetic and flap reconstructions) and a 24% incidence of wound complications. Cellulitis occurred in 2%, seromas in 12%, epidermolysis in 15%, and prosthesis loss in 4%.

The current study shows, as have previous studies, that wound complications occur frequently in breast surgery. The wound infection rate in this study is higher than the expected rate of 1% to 5% for a "clean" procedure.[10] It is also higher than noted in most other studies. However, the definition of infection used in this study includes many cases of "wound erythema" treated empirically with antibiotics. The majority of cultures yielded *Staphylococcus*, suggesting that empiric coverage with antistaphylococcal drugs in the face of wound infection is appropriate. Interestingly, the use of prophylactic antibiotics in either the MRM or MIBR group did not result in a significantly lower infection rate than nonuse and may be due to compromised blood flow to the skin flaps, causing erythema, or the small number of patients with infection available for comparison. This suggests, as in other "clean" procedures, that antibiotic prophylaxis may not prevent infection in breast surgery. However, it has been our practice to give prophylactic antibiotics to patients in whom a foreign body (breast prosthesis) is inserted. A recent prospective double-blind multicenter trial of prophylactic antibiotics in breast surgery found that the use of cefonicid sodium given to 303 patients undergoing breast surgery resulted in a wound infection rate of 6.6%, while 303 patients receiving placebo had a significantly higher wound infection rate of 12.2%.[11]

Age was shown to be a risk factor for infection in a National Academy of Sciences study[12] of 11 690 clean surgical wounds in which patients aged 45 to 55 years (n = 2339) had a wound infection rate of 4.9%, compared with a wound infection rate of 7.2% in 1818 patients aged 65 years and older. Our study shows that age greater than or equal to 60 years is a risk factor for infection in the MRM group, and a trend is observed in the MIBR group as well.

No risk factors could be identified for hematoma formation, which is probably a technical or comorbid-related complication. The data of the current study reveal a significantly higher incidence of seromas in the MRM than in the MIBR group, in patients aged 60 years or older (MRM group), in those whose drains were removed prior to drainage decreasing to 30 mL in 24 hours (MRM group), and in obese patients (MIBR group). The 30-mL volume was chosen because most surgeons at our institution use it as a guideline for the timing of drain removal. The lower seroma rate in the MIBR group was probably related to the significantly younger age of the women in this group. The lower rate did not seem to be related to the length of time drains were left in place. Axillary drains were left in place for a significantly shorter time in the MIBR group than in the MRM group. The mean volume of drainage in the 24 hours prior to drain removal was the same in both groups. Tejler and Aspegren[13] analyzed 313 women after MRM. The rate of seroma was not associated with the length of time drains were left in place. However, fewer seromas occurred when volume of drainage was less than or equal to 50 mL in the 24 hours prior to drain removal (32%), compared with greater than 50 mL (68%). They also found a positive correlation between seromas and increasing age, as did our study.

Our analysis of drainage volume as a risk factor for seroma revealed that in the MRM group, patients with drainage volume greater than 30 mL in the 24 hours prior to removal of the last drain had a significantly higher seroma rate (49% vs 24%). This suggests that drains should not be removed until volume is less than 30 mL/d. We have no explanation for the higher incidence of seromas in the older age group, except that wounds in older patients are known to heal more slowly (ie, form a drain tract), and have qualitatively decreased inflammatory response compared with younger patients.[14] In the MIBR group, eight of 48 patients had their drain removed when the volume was greater than 30 mL per day, yet none developed seroma. More patients may be necessary in the MIBR group before speculation on the effect of the implant on seroma rate can be made.

Obesity was found to be a risk factor for seroma within the MIBR group rather than within the MRM group. More obese women were in the MRM group and the rate of seroma was equal in the MRM group among obese and nonobese women. We have no explanation for why a younger obese woman with an implant has a higher risk of seroma, but perhaps drainage should be maintained longer in these women until a tract has formed.

The incidence of epidermolysis was significantly higher after MRM in smokers than in nonsmokers. Smoking has been shown in both animal and human studies to result in decreased flap survival secondary to the vasoconstrictive effects of nicotine on the cutaneous vasculature.[15-18] In the MIBR group, obesity was the only factor found to be associated with a significantly higher rate of epidermolysis. Say and Donegan[19] found that obesity and "large, fatty breasts" contributed to epidermolysis in cases of radical mastectomy; however, data in the literature with regard to obesity as a risk factor for wound complications following breast surgery are sparse.

We have demonstrated a lower wound complication rate in patients undergoing MIBR (31%) than in patients undergoing MRM (48%), which could be attributable to younger age and/or the lower seroma rate in the MIBR group. Patients in the MIBR group were younger, received prophylactic antibiotics more frequently, and had an earlier stage of breast cancer. The lower seroma rate is most likely due to increased pressure within the tissues from the breast prosthesis unless obesity is present. Our data suggest that MIBR is as safe with respect to wound complications as is MRM, with a smaller risk of seroma formation.

Immediate breast reconstruction following mastectomy provides women with breast cancer undergoing disfiguring surgery another option in their choices for therapy. It is our opinion that it should be offered to every woman undergoing MRM, particularly those who are not candidates for breast-conserving treatments. The data presented here with regard to the incidence of wound complications following breast surgery and the factors increasing risk for those complications will assist us to counsel our patients preoperatively, especially with regard to the effect of smoking on wound healing. Guidance is also provided as to timing of drain removal as related to drainage volume, age, or obesity.

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Discussion

H. STEPHENS MOSELEY, MD, Portland, Ore: In February 1980, Dr Robert Albo[20] and his colleagues described at this meeting 35 patients who had undergone immediate reconstruction over a 7-year period. Their criteria for selection of patients were as follows: (1) lesion less than 2 cm roentgenographically; (2) located in outer quadrants; (3) no clinically positive nodes; (4) in general, age less than 40 years; and (5) the mastectomy portion should be done by a surgeon with reconstruction done by a plastic surgeon. Several factors have led to the increasing acceptance of immediate reconstruction in the last decade. Most important is that we are seeing earlier breast cancer. Lumpectomy, axillary dissection, and postoperative radiation therapy has become widely accepted.

At Virginia Mason Clinic, MIBR is becoming a widely accepted procedure. How does this compare with lumpectomy, axillary dissection, and radiation?

I am surprised that seroma formation was twice as common in MRM than MIBR. Is this a function of the prosthesis acting as a reverse compression dressing, or is it related to the fact that older women have more seromas than younger women and more older women elected to have MRM?

Even with liberal criteria, only 14% of MIBRs and 12% of MRMs developed "infection," which is lower than many reports. Only five prostheses had to be removed and only two could be possibly related to infection and wound problems. What is the true infection rate in both groups?

H. CLARK HOFFMAN, MD, Seattle, Wash: The number of patients who had in situ carcinoma, stage I, stage II, stage III, and stage IV carcinoma were 13%, 42%, 37%, 7%, and 1%, respectively.

I consider patients with intraductal carcinomas, stage I carcinomas, and maybe even very early stage II carcinomas (ie, a lesion that is just barely over 2.0 cm in size, both with clinically negative nodes) to be ideal candidates for immediate reconstruction. I discourage any of my patients who have an advanced stage II, stage III, or stage IV disease from undergoing immediate reconstruction. In this group of patients, I prefer to get started with their chemotherapy or their hormone therapy as soon as possible and do not want to have any complicating factors arise from the immediate reconstruction that might delay this treatment. I usually advise them to wait at least 1 year, and then decide whether they want to undergo reconstruction. I have real concerns that 37% of your patients were in stage II.

The infection rate was the same in the modified mastectomy group who had prophylactic antibiotics as in those who did not. This fact strengthens my conviction that these patients do not need prophylactic antibiotics. However, in the immediate reconstruction, with the placement of prosthetic materials, all of these patients should be given prophylactic antibiotics to minimize the possibility of *S epidermidis* or *S aureus* infection. When the drainage is less than 30 mL, the drain can safely be pulled and will minimize seroma formation. I do not consider aspirating a few milliliters of seroma from the axilla a major complication.

Since you have shown us that this procedure can be done with no increased risk of complication, are you going to offer it to every patient who presents with a carcinoma of the breast, and particularly those with advanced stage II, stage III, or stage IV disease?

BALAZS I. BODAI, MD, Carmichael, Calif: Is reconstruction done by tissue expanders? If not, are you worried about compromising your margins of resection to preserve your flaps? Do you have any data regarding the number of lymph nodes that were removed in each of the two groups? The more lymph nodes removed, the more chance you have of getting lymphedema, and a higher chance of developing seromas.

We remove the drains when the drainage declines to about 100 mL per 24 hours. Our seroma formation rate is in the range of 10% to 15% in a very large experience. Do you not believe that immediate reconstruction decreases the ability to detect recurrences?

STEPHEN J. MATHES, MD, San Francisco, Calif: Is the implant placed with complete muscular coverage? Does this muscular coverage provide better muscle contact with the skin flaps? Does this reduce the seroma rate? Does this muscular coverage avoid implant removal for infection? Have you compared secondary procedures required in the MIBR group with those in the MRM group who have later elected breast reconstructive procedures? How does the quality of the results in delayed postmastectomy reconstruction compare with the immediate reconstruction group? What has the satisfaction level been in these two groups of reconstructed patients?

THEODORE X. O'CONNELL, MD, Los Angeles, Calif: I have three questions and concerns for the authors. Since the immediate reconstructive group was significantly younger, could this difference in age bias the observed complication rate?

This article proves that reconstruction does not have a negative impact on mastectomy, but does mastectomy have a negative impact on the reconstruction with respect to the complication rate, cosmetic excellence, etc? To decide whether immediate or delayed reconstruction is better, you need a third group of patients reconstructed at 6 to 12 months. From this report, one cannot conclude that mastectomy does not hurt reconstruction. What is the impact of infection when you do have a prosthesis present? Is the infection much more serious, and much more difficult to take care of, requiring parenteral antibiotics, and even removal of the prosthesis?

STEVEN N. PARKS, MD, Fresno, Calif: One of the comparisons that was not made was financial payor mix. Is the complication rate higher in those people who cannot afford to have immediate reconstruction? If we really have a lower complication rate, and if this is really a better way to do a mastectomy, maybe it would be better even if there is more extensive disease. It might be more cost-effective to do the immediate implant on all of our patients including those of a lower financial class.

DONALD L. MORTON, MD, Los Angeles: In my opinion, the indications for immediate reconstruction are questionable. Many of these women require continued revision of the prosthesis, so it is rarely done one time with no further procedures required. How many of your patients required additional operations related to the breast prosthesis or reduction mammoplasty on the other breast?

The indications for breast reconstruction are psychological. It is the woman's self-image and concern for how she is going to be accepted by her lover, her husband, her family, and society that make her very vulnerable during the period immediately before and after mastectomy. Thus, during this stress-filled period, almost all women indicate that they want to have reconstruction of the breast. As each month goes by, the patient realizes that she is still loved, that she is still desired, and her body image has not been totally devastated by this operation. She then begins to adjust to the altered body image. The proportion of women who want reconstruction drops with each postoperative month and levels off to only one in four or five women who eventually choose to be reconstructed. Until there is a properly paired study showing the psychological adjustment of women having immediate reconstruction vs delayed reconstruction that favors the immediate reconstruction group, this procedure should not be encouraged. This procedure, if performed routinely, is going to add to the cost of medical care and is not going to achieve much in terms of additional psychological benefit.

STEPHEN H. MILLER, MD, La Jolla, Calif: I am of the impression that these data do not show that reconstruction in patients with stage III or IV disease alters the ultimate course in these patients. Did the same surgeon perform the mastectomy in each case, and how many plastic surgeons were involved in the reconstructions? Could some of the differences have been due to differences in technique during the course of the mastectomy and/or reconstruction?

DR TRAVERSO: Our desire to preserve feminine form and self-image is paramount in offering this procedure as an option to women who have breast cancer. Do we compromise Halsteadian principles by trying to do immediate reconstruction? Does the silicone implant in itself cause cancer or increased infection? Does reconstruction delay adjuvant therapy or compromise detection of recurrent cancer? Do we disseminate disease in locally advanced tumors by placing a subpectoral implant with its larger dissection plane and therefore potentially contaminating the area where the implant goes?

The Mayo Clinic group reported in the ARCHIVES[21] this year on 108 patients with long-term follow-up after mastectomy and immediate breast reconstruction. Their analysis showed that an obligate number of the patients had recurrences, but no more so than would have been expected with mastectomy alone. When they did recur, the prognostic factors for recurrence were the same, ie, larger tumors, positive nodes, and estrogen receptors.

Dr Moseley, locally invasive cancer that invades the pectoralis major muscle, or is associated with grossly positive axillary nodes that might contaminate the new subpectoral dissection plane with tumor is a contraindication to reconstruction.

Relative contraindications are body habitus that might not give a good cosmetic result. Smoking and increased age are also relative contraindications. The 13% infection rate was found in both groups. This is a higher infection rate than is published in the literature because of our liberal definitions. Only 17% of what we called wound infections in the MIBR group had positive cultures, and 40% of the infections in the MRM group actually had positive cultures.

Dr Hoffman, I would not rule out the use of MIBR for stage III tumors per se, but because of what I saw during the dissection. We offer the procedure to almost all patients based on what we see during the operation. Patients understand that immediate reconstruction may not be performed. However, there is nothing better for a woman than to emerge from anesthesia and see a preserved breast mound. It is a most troubled time for these unfortunate women.

Dr Bodai, 57 of the 90 patients with MIBR had tissue expanders placed, and they all had successful final implants 3 months later. The number of lymph nodes that were removed in the MIBR group should not be different from those in the MRM group because every one of these 400 women underwent standard mastectomy. Modified radical mastectomy followed with reconstruction should not have changed the number of lymph nodes removed. In review of the 1989 results at the Mason Clinic for breast cancer, only 20% of our patients had positive lymph nodes; this is much lower than the national average.

Studies have shown that if the drain is removed before the volume falls below 50 mL in the last 24 hours, there is a significant association with seroma formation. Patients need to develop a tract and they need to heal and seal the flap as well as the axillary dissection. If the drain is removed before these factors have been accomplished, the risk of seroma formation is increased. Our data suggest that age is a risk factor for seroma, and that obese women seem to have an increased risk of seroma after MIBR regardless of what the drain volume is when it is removed.

Dr Mathes, the muscular coverage was complete in all of these patients. Eighty percent of patients with the reconstruction had preoperative antibiotics and the antibiotics were continued until the drains were removed in the MIBR group, but not in the MRM group. Approximately 40% of these women will request opposite breast reconstruction. Dr Morton, in regards to additional elective breast reconstruction, the follow-up of these patients with breast cancer is mandatory. They are never discharged from the medical system with or without reconstruction. Their participation in and additional expenses for medical care continue.

Dr O'Connell, the younger age of the MIBR group may falsely lower the wound complication rate. We state that MRM and MIBR are equal in safety. We do not wish to make any claims that MIBR is safer.

I agree with Dr Morton that a psychosocial comparison between the two groups has not been done, and it would be interesting, but the objectivity in the experimental protocol would be difficult to design. Dr Parks, I do not have any opinion on the financial-payor mix. Dr Miller, there were 12 general surgeons performing mastectomies and 4 plastic surgeons who did the reconstructions. One plastic surgeon did 80% of the reconstructions, and this variable should be considered when you evaluate our results.

The Hartmann Procedure

"It is usual, for cancer of the terminal portion of the pelvic colon, to do an operation which is quite severe, the abdomino-perineal resection. In two patients who had had colostomies after being obstructed, I have, as a second stage operation, resected the intermediate segment from the stoma to the rectum with its corresponding nerve supply. Then I have closed the proximal end of the rectum and I have reperitonealized it, leaving the perineum untouched. The postoperative course in both cases was as simple as that of our appendectomy. The preservation of a small subsphincteric rectal cul-de-sac has not created the slightest inconvenience. The patients are doing well after 9 and 10 months."

Commentary

Henri Hartmann capsulized in six sentences (113 words) a procedure that would require six pages for modern writers! Current program committees would probably reject it even as an abstract. Brevity, however, has its virtues. Virchow once remarked that "Brevity in writing is the best insurance for its perusal." The editor is indebted to M. Cristina Piancastelli, MD, for the translation of Hartmann's manuscript from French to English.

THE EDITOR

1. Hartmann H. *Chirurgie du rectum*. Paris, France: Masson et Cie; 1931

Analysis of Potential Risks Associated With 7.5% Sodium Chloride Resuscitation of Traumatic Shock

Mary J. Vassar, RN, MS; Colleen A. Perry, RN; James W. Holcroft, MD

• We evaluated the potential side effects of rapidly infusing 250 mL of either 7.5% sodium chloride or 7.5% sodium chloride per 6% dextran 70, using lactated Ringer's as the control, to 106 critically injured patients in two prospective double-blinded emergency department trials. Eight patients had a significant hyperchloremic acidemia in association with infusion of the hypertonic solutions, but all eight were moribund before infusion and many factors other than hyperchloremia could have contributed to their acidemia. Other blood chemistry changes that might have been associated with the hypertonic solutions, such as hyperosmolality or hypernatremia, were made insignificant by other factors, such as high blood alcohol levels or concomitant administration of sodium bicarbonate. There were no cases of central pontine myelinolysis; bleeding was not potentiated. There was no difficulty with crossmatching of blood. No anaphylactoid reactions occurred. In a setting of limited volume resuscitation, the solutions are likely to have a favorable risk-to-benefit ratio.

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Hypertonic saline,[1] which is now usually combined with a colloid volume expander to produce a typical 7.5% sodium chloride (NaCl)/6% dextran 70 solution,[2] can dramatically resuscitate animals that have been subjected to hemorrhagic shock, even when given in very small volumes. The hypertonic saline–dextran 70 formulation also appears promising for resuscitation of trauma patients in the prehospital setting, where intravenous administration of large volumes of fluids is impossible.[3,4] The solutions, however, could cause several complications. A rapid increase in plasma osmolality or sodium concentration, especially if sustained and if developing in a chronically debilitated patient with preexisting hyponatremia, could produce central pontine myelinolysis.[5] Rapid expansion of the plasma volume without concomitant potassium replacement could produce hypokalemia,[6] which could cause an arrhythmia. An increased plasma chloride concentration could produce metabolic acidemia that could compromise cardiac function or cause arrhythmia. Rapid reestablishment of blood volume and blood pressure combined with hyperosmolar shrinkage of an injured brain[7-12] could precipitate intracranial hemorrhage[13] and potentiate nontamponaded bleeding, like that caused by penetrating injuries or by injuries to the spleen or to the intraperitoneal portion of the liver.[14-16]

We have now completed three prospective clinical trials and are conducting two more with hypertonic saline in trauma patients. Of the five trials, three have been or are in the prehospital use of 7.5% NaCl/6% dextran 70; two have been in the use of hypertonic saline in the emergency department. These hospital-based trials, conducted under conditions of good lighting and in a setting where blood samples could be fairly easily obtained, have given us an excellent opportunity to evaluate the potential side effects of using hypertonic saline solutions for the resuscitation of trauma patients.

This report describes the results of our two emergency department trials. Both were controlled, randomized, and double-blinded. The first compared conventional isotonic resuscitation by lactated Ringer's (LR-1) with that by 7.5% NaCl without dextran (hypertonic saline [HS]); the second compared conventional lactated Ringer's (LR-2) with 7.5% NaCl/6% dextran 70 (hypertonic saline–dextran 70 [HSD]). The emphasis in this report is on an analysis of potential side effects of either HS or HSD resuscitation.

PATIENTS AND METHODS

Trial 1

Fifty-nine injured patients were entered into a controlled, randomized, double-blinded clinical trial that began in September 1986 and ended in April 1987. Patients with a systolic blood pressure of 90 mm Hg or less received as their initial resuscitation fluid 250 mL of LR-1 or 250 mL of 7.5% NaCl (HS), which were administered over a period of 1 to 5 minutes in conjunction with additional conventional isotonic fluids (usually lactated Ringer's) as the patient's condition warranted. The solutions were prepared by the hospital pharmacy and hung in the emergency department in coded bottles, available for immediate use. The bottles were identical; none of the medical personnel caring for the patients had knowledge of the treatment group.

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Patients who appeared to be less than 18 years of age and pregnant women were excluded from the study because an adverse side effect in a child or in a pregnant women in 1986, early in our clinical experience, probably would have set back our clinical trials by several years. Patients with known severe preexisting cardiac, hepatic, or renal disease were also excluded. Venous blood samples and, in many cases, arterial blood gas measurements, were obtained shortly after infusion of the test solution was started, within 15 minutes in 75% of the patients. Laboratory data are reported only for those patients who had initial blind samples obtained within 30 minutes from the beginning of test solution infusion. Serum osmolalities were measured by freezing point depression in many cases but not always. When not measured directly, they were calculated by the following formula:

$$\text{Osmolality} = 2(\text{Sodium} + \text{Potassium}) + (\text{Glucose}/18) + (\text{Serum Urea Nitrogen}/6) + (\text{Alcohol}/5),$$

in which serum concentrations of sodium, potassium, glucose, serum urea nitrogen, and alcohol are measured in millimoles per liter and nanomoles per liter, and osmolality is expressed as millimoles per kilogram. Revised trauma scores[17] were calculated using the first measurements obtained on admission to the emergency department. Injury severity scores[18] were coded from descriptions of injuries found on physical examination or at operation, from radiology reports, and from autopsies in those patients who died (all deceased patients had autopsies). The incidence of central pontine myelinolysis and intracranial hemorrhage was determined from macroscopic neuropathologic descriptions. Scoring and injury assessments were done without knowledge of the patient's treatment.

Trial 2

Forty-seven patients were entered into a second trial that was identical to the first except that the hypertonic solution was given in a 6% dextran 70 vehicle so that the final composition of the solution was 7.5% NaCl/6% dextran 70. In addition, the blood pressure entry criterion was lowered from 90 mm Hg to 80 mm Hg. The study ran from April 1987 to May 1988.

Statistical Analysis

Data are presented as mean ± SEM. Determination of differences between groups was made by a two-tailed Mann-Whitney test. Multiple linear regression was used for analysis of the continuous variables of osmolality, pH, and blood loss. Logistic regression was used in analyzing the effects of treatment group on mortality; significance was accepted at $P<.05$. Power calculations were made by the method and tables of Fleiss.[19]

The study was approved by the Human Subjects Review Committee of the University of California, Davis. Informed consent was waived because of the inability to provide adequate information before treatment needed to begin.

RESULTS

One hundred six patients were entered into the two protocols. Approximately 104 additional patients who met the blood pressure criterion were not entered during this same period: approximately 16 patients were excluded because they appeared to be less than 18 years of age; six patients were excluded because of pregnancy; six were excluded because of preexisting cardiac, hepatic, or renal disease, as indicated by a Medic Alert bracelet or by the presence of ascites or pedal edema found on physical examination; and 76 patients who met the criteria for the studies were not entered because in the urgency of resuscitation, their physicians forgot about the protocol.

The conditions of the patients entered into the two protocols are indicated in the Table. The four groups were comparable, but there was substantial variability within each of the four groups, as indicated by the large SEs. The mean injury severity score for the entire group was 29 ± 2. Of the 106 patients, 21 were under cardiopulmonary resuscitation when the test solution was first administered. The rate of administration of fluids other than the test solutions (most of the patients had more than one intravenous catheter in place) averaged 6.4 ± 0.7 L/h.

There were no significant differences in osmolalities between the HS and HSD groups and their respective control groups at any of the time periods, but severe hyperosmolality with a serum osmolality of 350 mmol/kg was found in 20 of the patients with the first blood sampling (Fig 1). Five of these 20 were in the LR-1 group, nine were in the HS group, three were in the LR-2 group, and three were in the HSD group. In 18 of these patients, the serum ethanol concentrations were 39 nmol/L or higher, accounting for at least 36 mmol/kg of the total osmolality. Repeated measurements (Fig 1) in 14 of these patients showed that the osmolality had decreased to less than 350 mmol/kg within 4 to 8 hours. In another patient in whom repeated measurements were available, the osmolality was less than 350 mmol/kg within 24 hours. Ethanol concentration and serum osmolality correlated well ($r^2 = .47$; $n = 48$; $P<.001$).

Two of the 20 patients with osmolalities of 350 mmol/kg or more did not have elevated ethanol levels. The first received HS and had an osmolality of 371 mmol/kg and an ethanol concentration of 4 nmol/L. The blood sample was obtained 1 minute after the infusion. He exsanguinated before additional measurements could be obtained. The second patient was in the LR-2 group and had an osmolality of 357 mmol/kg, an ethanol level of 8 nmol/L, and a serum sodium level of 169 mmol/L. He was under cardiopulmonary resuscitation and had received two intracardiac injections of 7.5% sodium bicarbonate at 5 and 3 minutes before the laboratory specimens were collected. He died before additional measurements were obtained

Of the 20 patients with initial extreme hyperosmolality, seven died. Autopsies in these seven showed no evidence of central pontine myelinolysis. (There was no evidence of central pontine myelinolysis in any of the 52 patients who died.)

There were no significant differences in serum sodium concentrations between the experimental groups and their respective controls, but severe hypernatremia, defined as a sodium concentration of 160 mmol/L or higher, was found in the first blood sample in three patients; one each in the HS, LR-2, and HSD groups (Fig 2). The HS patient with a serum sodium level of 167 mmol/L had a serum osmolality of 363 mmol/kg and an ethanol concentration of 112 nmol/L. The 4-hour sodium measurement was 154 mmol/L. The LR-2 patient had a serum sodium level of 169 mmol/L and had received intracardiac sodium bicarbonate. (He was described above in the paragraph on hyperosmolality.) The highest serum sodium level of 178 mmol/L was found in a nonsurviving HSD patient who arrived in the emergency department under cardiopulmonary resuscitation with a hematocrit of 0.07, an osmolality of 323 mmol/kg, and a pH of 6.48.

There were no significant differences in the serum potassium concentrations during any of the time periods, but severe hypokalemia, defined as a potassium level below 3.0 mmol/L, was found in 10 patients in the first time period (Fig 3). No arrhythmias were associated with the hypokalemia in any of the 10. No arrhythmias developed in association with infusion of test solutions in any of the patients. With the exception of one LR-1 patient, all of the potassium concentrations returned to normal within 4 hours.

The serum chloride concentrations in the HS group were significantly higher than those in the LR-1 group during the first sampling period (106 ± 1 vs 113 ± 2 mmol/L; $P<.05$), but this difference was resolved by the later time periods (Fig 4). Severe hyperchloremia, defined as a chloride concentration of 120 mmol/L or higher, was found in a total of 11 patients in both studies; seven were found in the HS group, one in the LR-2 group, and three in the HSD group. One of the HS patients died of exsanguination before additional measure-

Clinical Characteristics of Patients Receiving Lactated Ringer's in the First Trial (LR-1), 7.5% Sodium Chloride Without Dextran (HS), Lactated Ringer's in the Second Trial (LR-2), and 7.5% Sodium Chloride With 6% Dextran 70 (HSD)

	Study 1		Study 2	
	LR-1	**HS**	**LR-2**	**HSD**
No. of patients/Age, y	27/38 ± 3	32/32 ± 2	24/33 ± 3	23/35 ± 3
Mechanism of injury (blunt/penetrating), No.	11/16	17/15	17/7	10/13
Revised trauma score	4.8 ± 0.6	4.7 ± 0.5	3.4 ± 0.6	4.0 ± 0.6
Injury severity score	26 ± 3	28 ± 3	36 ± 4	29 ± 4
Patients receiving cardiopulmonary resuscitation when infusion started	6	4	4	7
Patients with no obtainable blood pressure (but not receiving cardiopulmonary resuscitation)	1	6	5	2
Time from injury to start of infusion, min	50 ± 7	50 ± 8	53 ± 5	42 ± 4
Rate of fluid administration in emergency department, L/h	5.3 ± 0.9	6.5 ± 1.4	7.4 ± 2.0	6.4 ± 1.0
Systolic blood pressure before infusion, mm Hg	62 ± 7	58 ± 7	55 ± 8	52 ± 8
Systolic blood pressure after infusion, mm Hg	80 ± 9	82 ± 7	74 ± 10	71 ± 9
Mortality, No. (%)	10 (37)	17 (53)	13 (54)	12 (52)
Deaths caused by injury to central nervous system	3	4	7	3
Deaths caused by hemorrhage	6	6	4	8
Deaths caused by multiple organ failure	1	7	2	1
Patients with intracranial hemorrhage				
No./Age, y	5/32 ± 9	8/38 ± 8	10/28 ± 8	5/34 ± 12
Revised trauma score	1.6 ± 0.7	3.4 ± 0.8	1.7 ± 2.0	3.7 ± 0.5
Injury severity score	44 ± 11	41 ± 6	48 ± 6	46 ± 10
Blood pressure before infusion, mm Hg	59 ± 16	55 ± 13	53 ± 12	68 ± 3
Blood pressure after infusion, mm Hg	78 ± 35	84 ± 14	62 ± 12	79 ± 8
No. of deaths	5	8	9	5
Patients with nontamponaded injuries				
No./Age, y	20/37 ± 3	23/33 ± 3	14/31 ± 2	17/31 ± 4
No. with liver or spleen injuries	9	9	11	10
No. with penetrating injuries	16	15	7	13
Revised trauma score	5.1 ± 0.7	4.5 ± 0.6	3.4 ± 0.7	4.0 ± 0.7
Injury severity score	24 ± 3	27 ± 3	37 ± 5	27 ± 4
Blood pressure before infusion, mm Hg	60 ± 8	55 ± 8	55 ± 12	44 ± 10
Blood pressure after infusion, mm Hg	80 ± 10	78 ± 10	67 ± 14	70 ± 11
No. who had an operation	14	17	10	14
Operative blood loss, L/h	1.2 ± 0.4	2.1 ± 0.8	2.3 ± 1.2	2.4 ± 0.9
No. with blood loss ≥1 L/h	6	7	4	5
No. of deaths	7	11	7	8

ments were obtained; in four of the HS patients, the severe hyperchloremia was resolved within 4 to 8 hours. In the remaining two HS patients, the 4-hour chloride levels remained elevated at 125 and 139 mmol/L. The first of these two patients died at 6 hours of exsanguination; the second survived, and the chloride concentration fell to 114 mmol/L at 24 hours. The LR-2 patient with initial severe hyperchloremia (127 mmol/L) was the patient described above who had a sodium level of 169 mmol/L and an osmolality of 357 mmol/L. Of the three HSD patients with initial severe hyperchloremia, one died before additional measurements were obtained; in the second patient, the chloride was normal at 4 hours; the third patient died of exsanguination at 10 hours with a chloride concentration of 120 mmol/L.

The systemic arterial pH in the HSD group was significantly lower than that in the LR-2 group during the initial sampling period (7.06 ± 0.07 vs 7.24 ± 0.03, $P<.05$). This difference was resolved by the later time periods (Fig 5). In the initial time period, severe acidemia, defined as a pH below 7.20, was found in a total of 24 patients: two in the LR-1 group, eight in the HS group, six in the LR-2 group, and eight in the HSD group. Sixteen of the 24 patients were either receiving cardiopulmonary resuscitation or had no obtainable blood pressure at the time of measurement; of these 16, 13 died. Of the 16, two were in the LR-1 group, four were in the HS group, four were in the LR-2 group, and six were in the HSD group. Of the remaining eight patients, the acidemia could be explained, at least in part, by either prolonged field times, prolonged hypotension in the field, hypothermia, decreased oxygen-carrying capacity of the blood (hematocrits of 0.20), or respiratory acidosis. (These data are available in tabular form from the authors on request.)

Simple linear regression of pH vs chloride concentration showed a weak correlation ($r^2 = .14$; $n = 45$; $P<.01$), and eight patients were both severely acidemic (pH, <7.20) and severely hyperchloremic (serum chloride concentration, ≥120 mmol/L). Of these eight, four were receiving cardiopulmonary resuscitation when the infusion was started, two were not receiving cardiopulmonary resuscitation but had no obtainable blood pressure, one was hypothermic (33.2°C), and

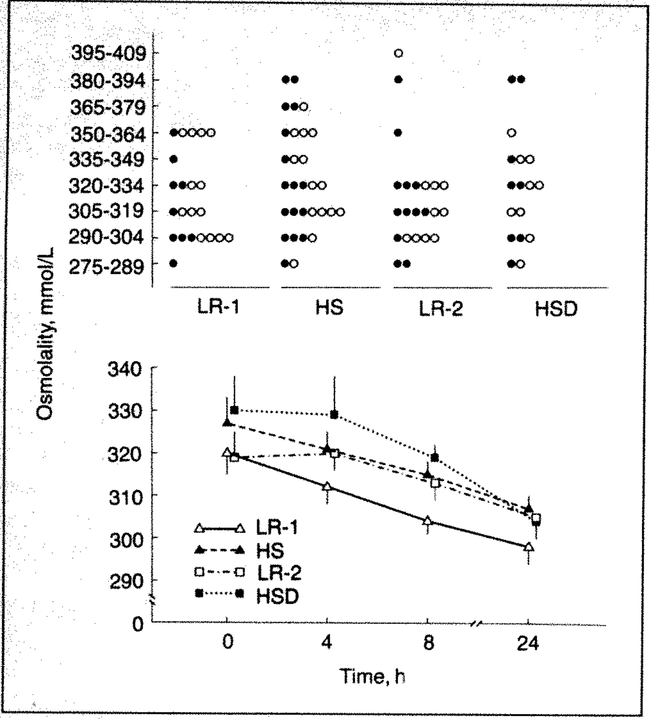

Fig 1.—Top, Serum osmolalities for initial blood samples. LR indicates lactated Ringer's; HS, hypertonic saline; and HSD, hypertonic saline–dextran 70. Closed and open circles represent values in patients who died and those who survived, respectively. There were no significant differences between the groups. Bottom, Osmolalities over 24 hours. The 0 hour values are the means and SEMs for the values depicted in the upper panel for 91 patients. Samples were available in 64 patients at 4 hours, 55 patients at 8 hours, and 60 patients at 24 hours. Vertical bars indicate SEMs.

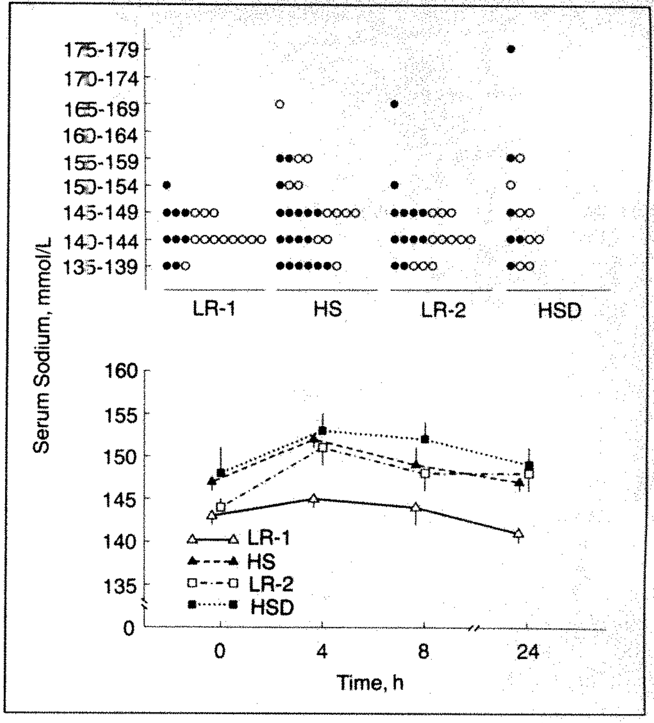

Fig 2.— Serum sodium concentrations. Top, See legend of Fig 1 for explanation of symbols and abbreviations. Bottom, Samples were available in 88 patients at 0 hours, 64 patients at 4 hours, 55 patients at 8 hours, and 60 patients at 24 hours. There were no significant differences between the groups at any time.

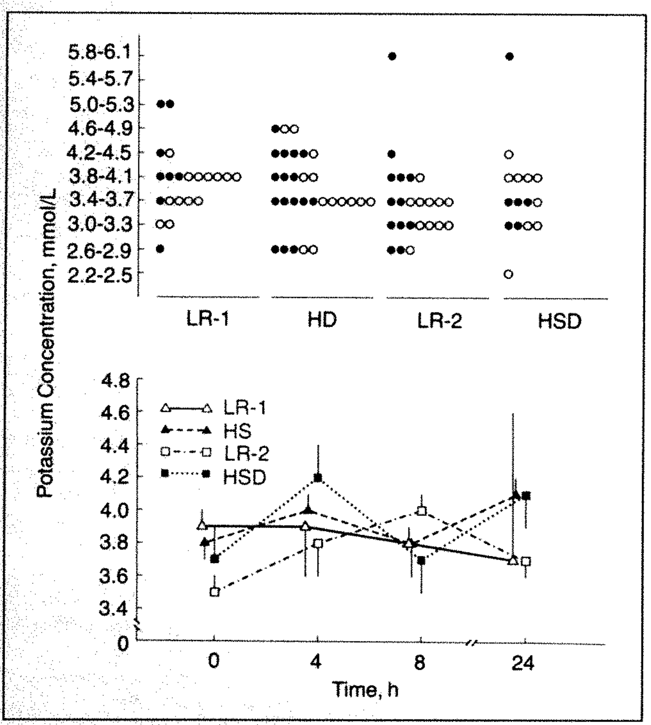

Fig 3.—Potassium concentrations. Top, See legend of Fig 1 for explanation of symbols and abbreviations. Bottom, With three exceptions, the numbers of samples available for analysis were the same as for the sodium measurements. There were no significant differences between the groups at any time.

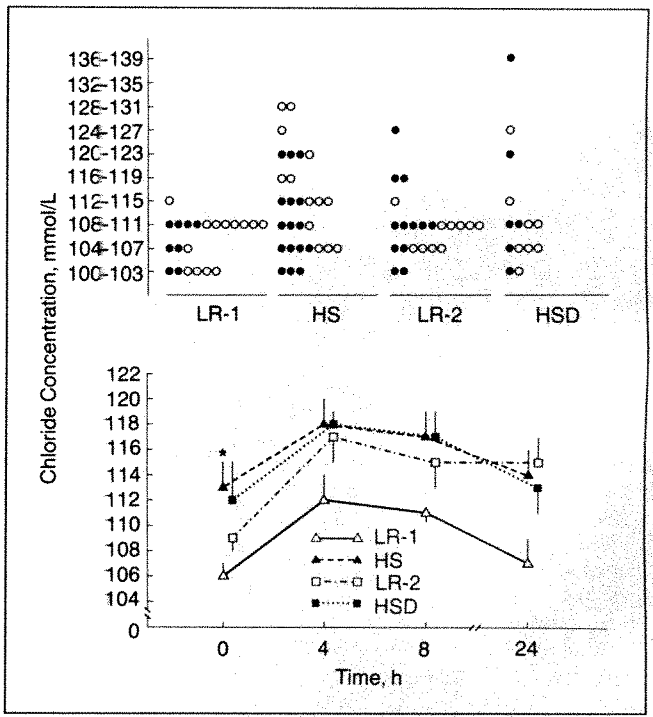

Fig 4.—Chloride concentrations. Top, See legend of Fig 1 for explanation of symbols and abbreviations. Bottom, The numbers of samples available for analysis were the same as for the sodium measurements. The chloride concentrations in the HS group were significantly higher than in the LR-1 group in the period after infusion ($P<.05$). There were no other significant differences.

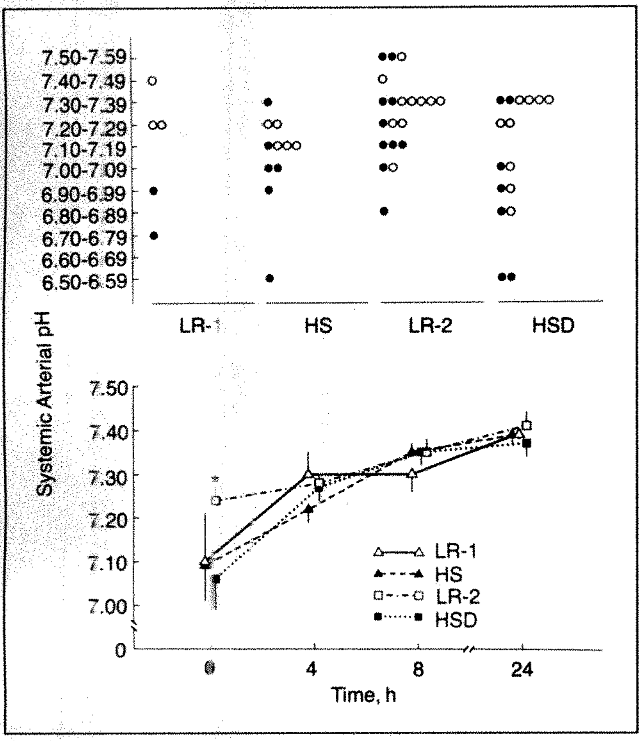

Fig 5.—Systemic arterial pH. Top, See legend of Fig 1 for explanation of symbols and abbreviations. Bottom, Samples were available in 52 patients at 0 hours, 64 patients at 4 hours, 52 patients at 8 hours, and 53 patients at 24 hours. The pH in the HSD group was significantly lower than that in the LR-2 group in the initial period after infusion ($P<.05$). There were no other significant differences.

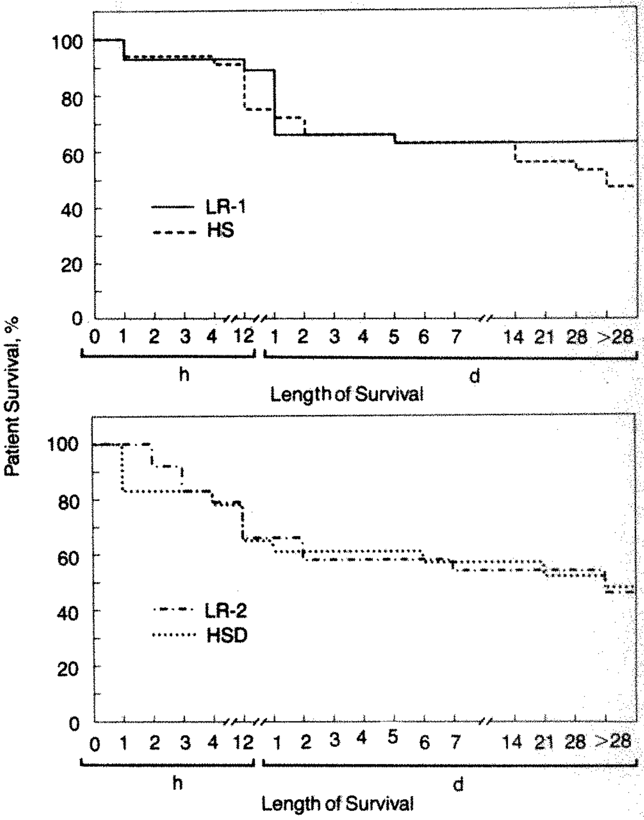

Fig 6.—Survival in the four groups. Top, LR-1 and HS. Bottom, LR-2 and HSD. There were no significant differences between the groups.

one had a hematocrit of 0.18. With multiple linear regression (taking into account not only chloride concentration, but also admission blood pressure, revised trauma score, injury severity score, cardiopulmonary resuscitation, time from injury, and hematocrit), the correlation between pH and chloride concentration became insignificant (complete data sets were available for 45 patients).

The blood pressure responses, as indicated by the increase in the systolic pressure from before the infusion to the first measurement made after the infusion ran in, were comparable between the groups (Table). There were no differences in overall survival between any of the groups by analysis of Kaplan-Meier constructions (Table and Fig 6). The overall mortality in the first study was higher in the HS group (53%) than in its corresponding control group (LR-1, 37%), but the difference was not statistically different. The mortality between the two groups was equivalent during the first 7 days; the overall long-term difference was accounted for by seven late deaths in the HS group that were caused by multiple organ failure. The mortalities in the LR-2 group (54%) and HSD group (52%) were comparable. Mortality correlated by logistic regression with the revised trauma score ($t=-3.2$, $P<.005$) and with the injury severity score ($t=2.3$, $P<.025$); it did not correlate with the treatment group.

The incidence of intracranial hemorrhage was equivalent between the treatment groups in the two studies (Table). Of the 28 patients who suffered intracranial hemorrhage, there were no cases in which hemorrhage occurred in the absence of clinical evidence for craniocerebral trauma. With the exception of one LR-2 patient, all of the patients in this category died.

The number of patients with nontamponaded injuries, that being any injury to the liver or spleen or any penetrating injury to any part of the body, were comparable between the groups (Table). Although not statistically significant, the blood loss in the HS group was somewhat larger than that in the LR-1 group (2.1±0.8 vs 1.2±0.4 L/h). This apparently larger loss was accounted for by two HS patients who each had total blood loss of more than 15 L. The largest blood loss in the LR-1 group was 8 L. Blood loss was not associated with the addition of dextran 70 to the hypertonic saline solution. Blood losses in the LR-1 and HSD patients with nontamponaded injuries were 2.3 and 2.4 L/h (Table). Blood loss correlated, by multiple linear regression analysis, with the injury severity score ($P<.007$; $n=78$); it did not correlate with the treatment group. There were no difficulties with crossmatching of blood in any of the patients. There were no anaphylactoid reactions to the dextran 70.

COMMENT

In summary, in two prospective trials in a hospital setting in which observation and opportunities for blood sampling were optimal, we could detect no adverse effects of rapidly infusing 250 mL of either 7.5% NaCl or 7.5% NaCl/6% dextran 70; nor could we detect any beneficial effects, probably because it was possible to gain large venous access quickly in these patients and infuse large volumes of fluid at rapid rates, an average of 6.4 L/h. The solutions will probably have their most prominent beneficial effect, if they are to have a beneficial effect at all, in those situations in which it is impossible to give large volumes of fluid, as in the prehospital setting for trauma patients.

Many of the patients were hyperosmolar, but their hyperosmolality was caused in many cases by high ethanol levels. There were no significant differences in the osmolalities between the various treatment groups. Larger sample sizes would be necessary to demonstrate a difference. For example, the osmolalities in the LR-2 and HSD groups were 319 ± 30 and 329 ± 32 mmol/kg. Documenting the significance of a difference of this magnitude, assuming that the means and SEs remained unchanged, would require a series of 400 patients in each group. Neither were there any significant differences between the serum sodium concentrations in the four groups. Documenting the significance of the observed difference would require individual group sizes of approximately 60 patients each.

There were significant differences in the serum chloride concentrations and systemic arterial pHs between the groups immediately after infusion, and there was a weak correlation between pH and chloride values. Severe acidemia, however, in all cases was associated with confounding preexisting clinical conditions other than hyperchloremia, such as cardiopulmonary arrest or hypothermia, and less severe acidemia was not associated with any adverse clinical events. All of the less severely acidemic patients had normal sinus rhythms and none showed signs of myocardial depression. In fact, hypertonic resuscitation in the setting of limited volume administration is associated with higher blood pressures than those obtained with lactated Ringer's resuscitation.[3]

Mortality was not significantly different between the groups, although the HS group's mortality was higher than that in the LR-1 group. This difference was accounted for by a number of late deaths in the HS group. Documenting the significance of the observed difference in the overall survival rates would require approximately 180 patients per treatment group. We can think of no reason why 7.5% NaCl should cause late mortality. Mortality correlated with the revised trauma scores and injury severity scores ($P<.05$ for both scores) as expected. It did not correlate with treatment group.

There was no evidence of potentiation of intracranial bleeding. Neither were there any cases of central pontine myelinolysis, but we excluded a few patients with the stigmata of severe preexisting disease from the trials. Central pontine myelinolysis has only been described with the rapid infusion of a hypertonic solution to chronically debilitated patients who then have had a prolonged period of hyperosmolality or hypernatremia. Our patients were probably at minimal risk because of their previous good health, in most cases, and because of the short duration of their hyperosmolality or hypernatremia (Figs 1 and 2).

There was no evidence of potentiation of bleeding from nontamponaded injuries. Bleeding was best explained by the injury severity scores ($P<.007$), not by treatment group. Rapid expansion of the blood volume is unlikely to precipitate bleeding in a severed blood vessel if a clot has had adequate time to form; 15 or 20 minutes between injury and fluid administration should be enough. Nontamponaded lacerations of vessels that are too large to be occluded by a clot are likely to be fatal if medical help is not immediately available; few of these patients will be entered into trials with hypertonic saline.

Last, there was no evidence of any side effects with the dextran 70 component of the HSD solution.[20] Bleeding was not potentiated, probably because the total amount of dextran 70 given to these patients (15 g) was well within the recommended maximum daily dose of 1.2 g/kg of body weight[20]; neither did the dextran 70 interfere with crossmatching, probably because of advances in blood bank crossmatching practices.[20,21] Severe anaphylactoid reactions to modern dextran formulations are rare, an incidence well below one per 1000 per unit infused[22,23] and, to our knowledge, have never been reported when the dextran has been used for acute resuscitation of trauma patients.

The lack of adverse effects in these two emergency department studies is consistent with toxicology studies in animals[24-26] and with accounts of patient resuscitation with hypertonic saline solutions.[3,4,27-29] If hypertonic saline resuscitation can be shown to benefit even a small proportion of patients, eg, in circumstances in which large volume resuscitation is impossible, it should probably be added to the therapeutic armamentarium. On the basis of these and other studies, and on the basis of theoretical considerations, they appear to pose little or no danger to the great majority of patients (with the exception being patients with chronic debilitating disease). The risk-to-benefit ratio of hypertonic saline solutions in the trauma setting is likely to be favorable.

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We thank Wayne Gannaway, PharmD, of the hospital pharmacy for preparing the solutions. We also thank the nurses and physicians who worked in the hospital emergency department during these two studies and who provided the emergency care for these patients.

The University of California, Davis, has a patent pending on the use of hypertonic saline/dextran solutions in resuscitation of shock. Dr Holcroft is one of the coinventors on the patent application.

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Discussion

C. JAMES CARRICO, MD, Seattle, Wash: Dr Holcroft and his associates were not able to demonstrate any adverse effects when 250 mL of one of these hypertonic solutions was the initial step in standard resuscitation with isotonic fluids and blood components. However, neither were they able to demonstrate any benefit from the administration of either hypertonic solutions under the conditions of the study.

This raises several issues. Were the numbers of patients sufficient to show either benefit or potential hazard? The 106 patients were randomized into four groups of approximately 25 to 30 each. Do you have any idea of the power of the data? Had there been either a difference in benefits or in complications, and what is the probability that you would have been able to detect it?

If we accept the idea that, despite the potential for some statistical haggling, there was, in fact, no difference in complications or in efficacy; one has to ask if this was a valid test. Since the total amount of hypertonic fluid administered was so small (compared with the remainder of the resuscitative fluid) that any benefit was disguised, would not any potential harm also have been disguised? The standard explanation of the benefit of these fluids is by their effect on osmolarity. Is there some other mechanism by which these fluids affect the circulatory system, or was the lack of impact on osmolarity presented in the study related to the lack of effect on the circulation? If you agree with the latter answer, did you really test the safety in any meaningful fashion?

Last, you concluded that hypertonic saline seems to have no role in resuscitation in the hospital setting where large amounts of isotonic fluid and blood can be administered. You proposed, instead, that hypertonic solutions can be of benefit in circumstances in which only small volumes are administered. Is that not the setting in which one should test safety as well? What can you tell us about safety in the prehospital setting? Of particular concern is what happens when multiple doses are administered. It may be easy to say that this should not happen, but we are all aware that under the difficult and sometimes desperate situations that occur outside of the hospital, it well might. What are the limits of safe administration of hypertonic fluids to injured patients? What happens if those limits are excluded?

FRANK R. LEWIS, JR, MD, San Francisco, Calif: In comparing the hypertonic group with the lactated Ringer's group in each of the two studies individually related to the amount of blood loss, you did not find a difference. Would it be valid to roll the two together and compare the hypertonic and the hypertonic dextran as one group with the lactated group? I suspect that would be statistically significant, indicating that blood loss would be increased by the use of the hypertonic solutions.

The question of resuscitation in prehospital care has been raised strongly in the last few months with Mattox's work in the military antishock trousers suit showing that patients who have bleeding above the diaphragm are probably made worse by raising their blood pressure. It has evoked a very old argument that goes back to the 1930s and 1940s about whether patients with holes in blood vessels ought to be resuscitated before they are in a position where a clamp can be put on the blood vessel. Your data would probably show that the answer would be that we should not be resuscitating them in the field.

C. JAMES CARRICO, MD, Seattle, Wash: It sounds like the seat belts are almost becoming the culprit in this deal. Certainly, there is a price for using seat belts, but I don't think there is any question that the benefit in terms of survival far outweighs the price.

Dr Blaisdell told us what to do when the colon is devascularized and what to do if it is perforated, but what is to be done when we find the colon with multiple areas of deserosalization? Should it be left alone or oversewn?

DR HOLCROFT: To demonstrate a difference in osmolality with values that we obtained would require 400 patients per group. To achieve statistical significance for the differences in sodium would require 60 patients per group. We did detect statistically significant differences ($P<.05$) in the chloride and in the pH.

Were these two trials valid for detecting abnormalities? Yes, particularly for detection of abnormalities that are likely to arise immediately after the infusion of the solutions. These emergency department trials are ideal ways to get these answers, and these results demonstrate that the solutions do not cause dangerous abnormalities. In terms of long-term complications and long-term survival, these trials do not answer the question. We have to wait until the prehospital trials are finished, which will be another 2 or 3 years.

We have not given multiple infusions to any of our patients, although I think an occasional patient might benefit from an additional dose.

Dr Lewis, if you lumped the two control groups together and compared their blood loss with that of the two hypertonic saline groups, the operative blood loss turned out to be a little bit less in the hypertonic group. The total operative blood loss in the lactated Ringer's group with nontamponaded bleeding was 4 L. The blood loss in the hypertonic group was 3.5 L. Dr Mattox's hypothesis is interesting, but there are few data to support it of which I am aware.

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While TIMENTIN is indicated only for the conditions listed above, infections caused by ticarcillin susceptible organisms are also amenable to TIMENTIN treatment due to its ticarcillin content. Therefore, mixed infections caused by ticarcillin susceptible organisms and β-lactamase producing organisms susceptible to TIMENTIN should not require the addition of another antibiotic.

ADVERSE REACTIONS: As with other penicillins, the following adverse reactions may occur: *Hypersensitivity reactions:* skin rash, pruritus, urticaria, arthralgia, myalgia, drug fever, chills, chest discomfort, and anaphylactic reactions. *Central nervous system:* headache, giddiness, neuromuscular hyperirritability or convulsive seizures. *Gastrointestinal disturbances:* disturbances of taste and smell, stomatitis, flatulence, nausea, vomiting and diarrhea, epigastric pain. *Hemic and Lymphatic systems:* thrombocytopenia, leukopenia, neutropenia, eosinophilia and reduction of hemoglobin or hematocrit. Prolongation of prothrombin time and bleeding time. *Abnormalities of hepatic and renal function tests:* elevation of serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), serum alkaline phosphatase, serum LDH, serum bilirubin. Rarely, transient hepatitis and cholestatic jaundice--as with some other penicillins and some cephalosporins. Elevation of serum creatinine and/or BUN, hypernatremia. Reduction in serum potassium and uric acid. *Local reactions:* pain, burning, swelling and induration at the injection site and thrombophlebitis with intravenous administration. *Overdosage:* As with other penicillins, TIMENTIN in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures. Ticarcillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding and pharmacokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by hemodialysis.

CONTRAINDICATIONS: TIMENTIN is contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH TIMENTIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER DRUGS. IF AN ALLERGIC REACTION OCCURS, TIMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE PROVIDED AS INDICATED.**

PRECAUTIONS: While TIMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, organ system functions should be assessed periodically during therapy.

Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics. These reactions have been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal impairment. If bleeding manifestations appear, TIMENTIN treatment should be discontinued and appropriate therapy instituted.

TIMENTIN has only rarely been reported to cause hypokalemia. Periodic monitoring of serum potassium may be advisable in patients receiving prolonged therapy.

Pregnancy (Category B): Reproduction studies have been performed in rats given doses up to 1050 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to TIMENTIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

DOSAGE AND ADMINISTRATION: TIMENTIN should be administered by intravenous infusion (30 min.). Usual recommended dose for systemic and urinary tract infections for average (60 kg) adults is 3.1 Gm TIMENTIN (3.1 Gm vial containing 3 Gm ticarcillin and 100 mg clavulanic acid) given every 4 to 6 hours. For gynecologic infections TIMENTIN should be administered as follows: Moderate infections 200 mg/kg/day in divided doses every 6 hours and for severe infections 300 mg/kg/day, based on ticarcillin content, in divided doses every 4 hours. For patients weighing less than 60 kg, the recommended dosage is 200-300 mg/kg/day, based on ticarcillin content, given in divided doses every 4 to 6 hours. In urinary tract infections, a dosage of 3.2 Gm TIMENTIN (3.2 Gm vial containing 3 Gm ticarcillin and 200 mg clavulanic acid) given every 8 hours is adequate. Please see official package insert for details on dosages for other patients, including those with renal insufficiency, and directions for use.

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[*] Efficacy for this organism in this organ system was studied in fewer than 10 infections. 7548/H–BS ©1989, Beecham Laboratories

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Blunt Intestinal Injury

Keys to Diagnosis and Management

David H. Wisner, MD; Yong Chun; F. William Blaisdell, MD

• Fifty-six patients with blunt intestinal injury seen during 39 months were reviewed for keys to diagnosis and treatment. Motor vehicle accidents were involved in 80% of the cases and seat/lap belts were in use 69% of the time. Blunt intestinal injury was the only abdominal injury in 70% of the cases. There were 42 perforations and 20 devascularizations; multiple injuries were common (27%). Abdominal tenderness was present on admission in 43 of 44 patients in whom a reliable examination was possible. Peritoneal lavage was positive in 13 (93%) of 14 patients. Computed tomography was falsely negative in three of four instances in which it was used. Perforations were most common in the upper and lower ends of the small bowel and in the sigmoid colon; devascularizations were most common in the distal ileum and sigmoid colon. Resection/anastomosis was performed in 38% of small-bowel perforations and in all small-bowel devascularizations. Resection/diversion was required in most colonic perforations (five of six patients) and devascularizations (four of six patients). There were five deaths (9%), none due to intestinal injury. There were seven complications related to intestinal injury. Diagnostic delay occurred in two patients; both had resultant morbidity. Blunt intestinal injury is associated with physical findings in conscious patients. Peritoneal lavage should be used when tenderness cannot be evaluated. Timely operative intervention minimizes morbidity and hospital stay.

(*Arch Surg*. 1990;125:1319-1323)

Intestinal perforation or devascularization from blunt trauma is an infrequent but serious injury. A number of series have reported on the frequency, characteristics, and treatment of blunt injuries of the intestine.[1-14] Many of these series are small or collections of experience from a number of centers. The definition of blunt intestinal injury (BII) has varied, including in some series serosal tears of the bowel and mesenteric hematomas that did not require surgery. Most series have concentrated on bowel perforations and have included few or no cases of bowel devascularization. Some have emphasized the importance of seat belts in the development of BII while others have found little correlation.

There is little disagreement about the need for rapid diagnosis and surgical treatment of blunt perforations or devascularization of the bowel, but much less consensus about how to make the diagnosis.[2,4,7,12-16] The relative merits of the physical examination, serum amylase determination, peritoneal lavage, and computed tomography are a matter of debate.

We retrospectively reviewed our recent experience with BIIsat a single institution with a high volume of blunt trauma injuries in an attempt to answer the following questions: (1) How frequent is serious BII at a trauma center where the majority of patients are seen primarily rather than in transfer from other institutions? What are the relative frequencies of perforation and devascularization of the small bowel and colon injuries? (2) How often does BII occur as the only injury that a patient suffers or as an isolated abdominal injury? (3) How important are seat belts as a possible causative factor in BII ? (4) What are the keys to the diagnosis of BII?

MATERIALS AND METHODS

The University of California, Davis, Medical Center, Sacramento, is a level I trauma center serving northern California. The trauma registry was used to review all patients with a blunt mechanism of injury admitted to the hospital during the 39-month period between April 1986 and August 1989.

Significant BII was defined as either bowel perforation or devascularization injury serious enough to require bowel resection. Mesenteric hematomas and lacerations were not included unless they required resection. Serosal tears, even if repaired, were also excluded.

Cases of significant BII were reviewed for the mechanism of injury, associated injuries, indications for abdominal exploration, operative procedures performed, postoperative complications, and discharge disposition. Vital signs, physical findings, roentgenograms, and laboratory results were also reviewed. The nature and location of the intestinal injuries were recorded. The use of seat-belt restraints at the time of injury was also noted when this information was available.

When computed tomography was used, double-contrast scans using intravenous and oral (or nasogastric) contrast were performed. Where appropriate, values are reported as the mean ± SEM.

RESULTS

Fifty-six patients fit the review criteria for the study, amounting to 0.7% of the total blunt trauma admissions during the review period and a mean of 1.4 patients per month.

Forty-two patients suffered perforations and 20 had devas-

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Table 1.—Associated Injuries

Injury	No. (%) of Patients
Extra-abdominal	
Rib/sternal fracture	18 (32)
Pelvic fracture	11 (20)
Cerebral concussion/contusion	10 (18)
Upper extremity fracture	10 (18)
Lower extremity fracture	9 (16)
Facial laceration	8 (14)
Lumbar spine fracture	7 (12)
Clavicle fracture	4 (7)
Basilar skull fracture	3 (5)
Cervical spine fracture	3 (5)
Facial fracture	3 (5)
Urethral disruption	2 (4)
Spinal cord contusion	1 (2)
Subdural hematoma	1 (2)
Intra-abdominal	
Liver laceration	14 (25)
Splenic rupture	8 (14)
Bladder rupture	2 (4)
Diaphragm rupture	2 (4)
Kidney rupture	1 (2)
Kidney devascularization	1 (2)
Pancreatic transection	1 (2)
Gallbladder avulsion	1 (2)
Iliac artery disruption	1 (2)
Superior mesenteric vein tear	1 (2)

Table 2.—Mechanism of Injury

Mechanism	No. % of Patients With Blunt Intestinal Injury	% of Patients With All Blunt Trauma
Motor vehicle	45 (80)	51
Motor vehicle vs pedestrian	5 (9)	14
Motorcycle	2 (4)	11
Assault	0	9
Fall	0	8
Bicycle	1 (2)	1
Other	3 (5)	6

cularizations. The sum of the two types of injuries was greater than the total number of patients because both perforation and devascularization injuries occurred in six patients. There were also nine cases in which multiple intestinal perforations occurred. In all, 15 patients (27%) had multiple intestinal injuries.

No associated injury of any kind, either extra-abdominal or intra-abdominal, was present in six patients (11%). The most common associated injuries in the remainder of the patients were thoracic wall trauma, pelvic fractures, closed head injury, and extremity fractures (Table 1).

Blunt intestinal injury was the only intra-abdominal injury found at exploration in 39 (70%) of 56 patients. In the remaining 30%, injuries to the liver and spleen were the most common associated intra-abdominal injury (Table 1).

Head injury was present in 10 patients (18%) and included five concussions and five cerebral contusions. All were due to motor vehicle accidents. Seat belts had been in use in five of the seven accidents in which the seat-belt status was known. There were seven lumbar spine fractures, five in motor vehicle–accident victims. Seat belts were in use in four of these five accidents.

Mechanisms of injury varied, but the majority of patients were involved in motor vehicle accidents (Table 2). The percentage of patients with BIIs that occurred in motor vehicle accidents was higher than for the blunt trauma population as a whole (80% vs 51%). Of the patients injured in motor vehicle accidents, their status as drivers or passengers was known in 43 of 45 cases; 26 (60%) of these 43 were drivers. Whether the patient was using a seat belt at the time of the injury was documented in 32 (71%) of the motor vehicle accident cases. A restraint was in use in 21 (66%) of these 32 cases. This compares with a 22% rate of seat-belt use for all victims of motor vehicle accidents admitted to our institution.

Results of the physical examination of the abdomen done on admission to the emergency department were documented in 44 patients. Abdominal tenderness was present in 43 (98%) of patients, and in 26 (60%) of these 43 patients it was diffuse. The admission abdominal examination results were not recorded in 12 patients. Of these 12 patients, nine had a Glasgow coma scale score of less than 8, one was a 2-year-old child, one had received a paralytic agent, and one was a paraplegic. A rectal examination was performed on admission in 41 patients and the results were positive in only two patients (5%).

Peritoneal lavage was carried out in 14 patients and was positive in 13 (93%). In nine of these patients, the lavage was grossly positive for blood[8] or feculent material.[1] In the remaining four patients, the red blood cell count in the lavage fluid was greater than 100×10^{12}/L in two patients and the white blood cell count was greater than 0.5×10^{12}/L in all four patients. Of these four patients in whom the diagnosis of intestinal injury was made with cell counts, three had perforations of the jejunum and one had a devascularization of the colon. The lavage amylase concentrations in the three patients with jejunal perforation were 131 U/L, 59 U/L, and 3 U/L.

Peritoneal lavage results were falsely negative in one patient. In spite of a perforation of the transverse colon, the red blood cell count was 0.41×10^{12}/L, the white blood cell count was 0.025×10^{12}/L, and the lavage amylase value was 3 U/L. The patient eventually underwent exploration because of persistent abdominal pain and tenderness.

The mean (± SEM) serum amylase value on admission was 83 ± 11 U/L for all patients. The mean value for patients with perforation (85 ± 13 U/L) was not significantly different from that for patients with devascularization injuries only (79 ± 24 U/L), although 10 of the 13 patients with abnormally high serum amylase concentrations (100 U/L) on admission had perforation injuries, and only three had devascularization injuries.

Computed tomography of the abdomen was performed in four patients, and was positive for intra-abdominal fluid in one patient with both a jejunal perforation and a sigmoid devascularization scanned shortly after admission. The other three scan results were interpreted as normal. All three patients had small-bowel perforations. Two were scanned within hours of admission and one was scanned on the second hospital day. All eventually underwent exploration because of persistent and increasing abdominal findings.

Findings on physical examination were the most common indication for abdominal exploration (Table 3). Many patients had more than one indication for exploration. There was only one case of duodenal perforation (Table 4). Small-bowel perforations tended to occur in the proximal jejunum or distal ileum. Colon perforations showed a predilection for the sigmoid colon. Devascularization injuries were evenly distributed between the small bowel and the colon, with the preponderance of injuries concentrated in the distal ileum and sigmoid colon.

Two patients had delays in diagnosis of longer than 2 days. One was a 2-year-old child involved in a motor vehicle accident. Results of an abdominal computed tomographic scan

Table 3.—Indications for Abdominal Exploration

Indication	No. (%) of Patients
Abdominal tenderness	41 (73)
Hemodynamic instability	15 (27)
Positive peritoneal lavage results	13 (23)
Falling hematocrit	7 (12)
Open pelvic fracture/perineal laceration	2 (4)
Positive computed tomographic scan results	1 (2)

Table 4.—Location of Injuries

Location	No. of Perforations	No. of Devascularizations
Duodenum	1	0
Jejunum		
Proximal	12	2
Mid	6	. . .
Distal	5	. . .
Not specified	5	1
Ileum		
Proximal	2	1
Distal	8	7
Colon		
Appendix	0	1
Cecum	1	0
Ascending	0	2
Transverse	1	1
Descending	0	0
Sigmoid	4	5

performed shortly after admission were negative. The patient required exploration on the seventh day after injury because of abdominal tenderness and distention. A perforation of the distal ileum with peritonitis was discovered, and that segment of the ileum was resected with proximal diversion. This postoperative course was complicated by fascial dehiscence and a pelvic abscess.

The other prolonged delay in diagnosis was in a 22-year-old male crushed in a tractor accident. A laparotomy done shortly after admission revealed a hematoma and contusion of the transverse colon, which were treated conservatively. Three and one half weeks later the patient returned to the operating room and underwent resection of that segment of the colon because of persistent gastrointestinal bleeding and diarrhea secondary to devascularization. Small-bowel perforations were repaired 58% of the time. The remainder required either resection and primary anastomosis (38%) or resection with diverting ileostomy (4%). All small-bowel devascularizations were resected with primary anastomosis.

Five of six colonic perforations were resected with proximal diversion. One perforation of the transverse colon was repaired primarily and the patient had an uneventful postoperative course. The appendix was devascularized in one patient and was resected. Six of the eight remaining patients with colon devascularization underwent resection with proximal diversion. One patient with a devascularization injury of the sigmoid colon underwent resection with primary anastomosis and no proximal diversion. He had an uncomplicated postoperative course. The other patient who underwent a resection with primary anastomosis had a devascularization injury of the ascending colon. Her postoperative course was complicated by sepsis and a wound infection. The results of a work-up for an intra-abdominal abscess were negative and she eventually improved and was discharged.

There were five deaths (9%). All were due to head injury and none was secondary to the intestinal injury. There were seven complications in six patients related to the intestinal injury (five wound infections and two intra-abdominal abscesses). One intra-abdominal abscess developed in a patient with a devascularization injury of the distal ileum who was treated with resection and primary anastomosis. The other abscess was in the patient described above with a delayed diagnosis of perforation of the distal ileum; it was ultimately treated with resection and diverting ileostomy.

COMMENT

Early recognition and treatment of BII is important in the prevention of morbidity.[2,4,7,12-16] This was confirmed in our series by the occurrence of serious complications in both patients with BII in whom lengthy diagnostic delays occurred. To our knowledge, only two previous series have detailed the rate of complications related to BII. Hunt et al,[9] in a series of 22 patients, reported a wound infection rate of 18% and an intra-abdominal abscess rate of 23% after blunt perforations of the gastrointestinal tract occurred.[9] Many of these patients had long delays between injury and diagnosis. Dauterive et al,[5] in a more recent report of 60 patients with either perforation or devascularization injuries, reported a 7% incidence of complications, which compares with the 11% incidence seen in our patients. All of the patients in the series by Dauterive et al underwent diagnostic peritoneal lavage on admission to the emergency department, and the vast majority were operated on quickly.

Serious intestinal injury is an infrequent complication of blunt trauma, but there are suggestions that the frequency has increased with increased numbers of patients being injured in high-speed motor vehicle accidents. Bosworth[2] found only 10 such cases in approximately 180 000 surgical admissions to New York area hospitals between the mid-1930s and mid-1940s. Only 30% of the injuries in this era were secondary to motor vehicle accidents. A more recent report of 6745 admissions to a referral trauma center during 5 years revealed a 0.9% incidence of serious BIIs, 77% of them due to motor vehicle accidents. These numbers are consistent with our data, collected between 1986 and 1989.

The role of seat belts in the pathogenesis of BII is unclear. Some reviews have emphasized the importance of seat belts,[1,14] but a number of other reports have found no correlation between seat belts and BII.[6,12,13] In one series of 16 patients with BIIs, none of the patients was known to be wearing a seat belt at the time of injury.[13] Our series suggests a role for seat belts in the pathogenesis of BII since they were in use in 66% of the motor vehicle–accident victims in whom the seat-belt status was known. A correlation between seat-belt use and BII should not discourage the use of seat belts, however, since they have been shown to improve morbidity and mortality from motor vehicle accidents by up to 35%.[17] Use of seat belts results in lower rates of serious head injuries, a major factor in determining outcome. All five deaths in our series were due to head injury, and a seat belt was in use at the time of injury in only one of these cases. The possibility of seat-belt injury of the intestine is more than offset by this increased risk of serious closed-head injury.

If early diagnosis and operative intervention are important, how can the diagnosis best be made? The value of the physical examination has been emphasized by some authors,[4,9,13] while others have stressed its lack of reliability.[3,8,14] Our results indicate that in patients who can cooperate with a physical examination, abdominal pain and tenderness are nearly always present when there is either perforation or devascularization of the bowel. These findings are present immediately after the injury.

In patients who cannot cooperate with a physical examination, peritoneal lavage is the diagnostic procedure of choice. A number of series have documented false-negative rates for diagnostic peritoneal lavage of between 1% and 20%. The rate in our series was 7%. Lavage red blood cell and white blood cell counts are the most important means of lavage diagnosis. The rate of false-negative amylase values in lavage fluid is high and the lavage amylase results should not be used to confirm or deny the presence of perforation.

Computed tomography was not used extensively in our series, but it had a distressingly high false-negative rate. Negative computed tomographic scan results should be interpreted cautiously, especially in a patient with tenderness on physical examination of the abdomen.[18]

This series emphasizes the high frequency with which intestinal injury is the only intra-abdominal injury after blunt abdominal trauma, and that BII can also occur as the only injury in a patient injured from blunt trauma. It also stresses the relatively frequent occurrence of multiple BIIs and the need to examine the entire length of the bowel at celiotomy, even if one area of injury is immediately identified.

Devascularization injuries to the small bowel showed a predilection for the proximal and distal bowel, which has been described previously and ascribed to the fact that the bowel is relatively fixed at these points. Perforation injuries were more widely distributed, which conflicts with the commonly held belief that they are also concentrated primarily at either end of the bowel.[13] Compression and distention as mechanisms of injury in perforation as opposed to traction and distraction as the mechanism of injury in devascularization may explain this difference in distribution.

The sigmoid colon was particularly vulnerable to both devascularization and perforation, possibly because it is located on a mesentery, is lower in the abdomen than the transverse colon, and is more vulnerable than the ascending or descending colon to compression against the vertebral column and traction or distraction of its mesentery.

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Discussion

NORMAN M. CHRISTENSEN, MD, Eureka, Calif: This series is one of the two largest in the literature. All patients had either a hole in the bowel or a devascularized bowel. The zero mortality in this series reflects the belief that the most important function of trauma organization is to ensure that patients do not die of relatively simple, treatable injuries. A physical examination in the conscious patient and a peritoneal lavage in cases in which the abdomen cannot be evaluated will lead to the correct diagnosis in almost 100% of patients.

The authors found that the determination of lavage amylase levels is worthless and abdominal computed tomography had a disturbingly high false-negative rate. Sherck and Oakes, in a review of 370 consecutive abdominal computed tomographic scans at the Santa Clara Valley (Calif) Medical Center, found that in none of the seven patients with intestinal injury was a preoperative abdominal computed tomographic scan diagnostic.

The authors hedge regarding the role of seat belts in intestinal injury, stating that their role is "unclear." This series "suggests" a role since seat belts were in use in 66% of the motor vehicle accidents in which seat-belt status was known. The literature documents that seat belts have contributed to the increase in intestinal injuries. In 1971, Jordan and Beall (*Curr Prob Surg.* 1971:5-9) reported that in cases of blunt abdominal trauma, 75% of patients had solid organ involvement, while 20% of the patients had intestinal involvement. This study was carried out before seat belts became popular or mandatory. In Canada, where seat belts are mandatory, reports from Vancouver General Hospital and the trauma unit at the University of Montreal show intestinal injury rates of 67% and 84%, respectively, for those patients wearing seat belts.

It is worth emphasizing, however, that seat belts *do* save lives, and it is worth remembering that in the historic Volvo study of 28 780 traffic accidents in Sweden, there were no fatalities at speeds up to 60 mph in front-seat passengers wearing seat belts, while fatalities occurred in riders who did not wear seat belts at speeds as low as 12 mph.

In the present study, 75% of the colon injuries were treated by resection and proximal diversion. This is an unusually large number of civilian colon injuries requiring diversion. Do you use abdominal computed tomography in the usual evaluation of patients with blunt abdominal injury? How can the diagnosis of BII in infants best be achieved? What was the usual time between presentation and diagnosis in these patients?

JACK H. BLOCH, MD, Bakersfield, Calif: Our experience has been that the three-point harness is the most common type of seat belt and does a good job of protecting the intrathoracic abdomen and the intrapelvic abdomen, but it leaves the central abdomen vulnerable. Too frequently, the lap portion of the seat belt creeps up onto the abdomen into a potentially dangerous position.

We see a large number of people who drive pickup trucks with lap belts only. The most common injury in this group is an upward shearing injury in which the belt leaves a stripe across the abdomen. If a three-point harness is worn, injuries frequently associated with the abdominal injury may be a left clavicular fracture, occasionally a shearing injury of the left cervical portion of the brachial plexus, and the usual injuries that occur in lower extremities, including ankle fractures, tibial fractures, and sometimes patellar fractures.

The constellation of injuries in victims wearing seat belts is very different from those in the unrestrained patient who has been ejected through the windshield, thrown out of the car door, or poked in the abdomen by some protuberance in the car, and usually sustains rib, spleen, and liver trauma. Among patients wearing seat belts we have seen very few solid visceral injuries. Have the authors had the same experience that we have had with the altered constellation of injuries? Second, a seat-belt stripe on the abdomen is really not innocuous. We have come to the conclusion that every patient with a seat-belt stripe should be admitted and observed overnight even if there is not sufficient clinical evidence to warrant diagnostic peritoneal lavage.

We have been unhappy with the diagnostic accuracy of computed tomographic scanning for bowel or mesenteric injuries and with the recent popularity of ultrasonography of the abdomen for free fluid. Frequently, after keeping the patient with a small tear or perforation overnight, even though the original clinical findings were not too obvious, as in acute appendicitis, many patients with small-bowel or mesenteric tears will have signs of acute peritonitis by the next morning. Would the authors comment on the seat-belt stripe phenomenon and whether such patients should be observed in the hospital or automatically operated on?

JONATHAN R. HIATT, MD, Los Angeles, Calif: The diagnosis of perforations and devascularizing injuries are somewhat different. Computed tomographic scanning with oral contrast will show a large hole in the upper gastrointestinal tract, but when these cases are analyzed closely, the patients usually have sufficient symptoms and signs to warrant a laparotomy on clinical grounds alone, particularly with a "seat-belt" sign. The seat-belt contusion is a compelling reason for closer evaluation with computed tomography or, probably better, peritoneal lavage. The devascularizing injuries may be more subtle at presentation and more difficult to diagnose at the outset of treatment.

I have encountered a medicolegal issue relating to seat belts. Do lap belts, which restrain passengers and certainly prevent the neurologic injuries that may result if the passenger is thrown from the vehicle, cause abdominal injuries? Is the air bag a better safety system?

DON R. MILLER, Irvine, Calif: A rare lesion resulting from blunt trauma is late ischemic stricture. A van rolled over, and the patient walked more than a mile after the injury, with no physical findings except for the presence of a seat-belt abrasion. Nothing was done at that time, but weeks later he presented with a small-bowel obstruction, and surgery disclosed an ischemic stricture due to an opening in the mesentery, which was only 2 cm in diameter. Simple resection of the stricture was required. Did you have any late injuries?

DR BLAISDELL, MD: Seventy-five percent of our patients were treated with proximal colostomy, and this reflects our conservative attitude toward these blunt types of injuries. When dealing with penetrating trauma and minimal contamination, we tend to suture the injury primarily. This is associated with minimal morbidity despite previous wartime experience, which suggested that under military circumstances a colostomy is the procedure of choice. Blunt trauma, however, is a devascularizing type of injury and tends to spread contamination around; hence our conservatism.

Our experience reflects my negative bias regarding the use of computed tomography. Some centers perform computed tomography on all their patients as they come through the emergency department The problem is that the earlier one does the examination, the more apt the results are to be negative. Computed tomography results become positive when a lot of blood has accumulated or when the contamination has resulted in the establishment of peritonitis. If you perform these studies within an hour of injury, the result may not yet be positive.

The other problem with computed tomography is that it removes the patient from observation in the first hour after injury. The advantage of lavage is that one can keep the patient under observation. If anything happens to the patient, he or she can be taken promptly to the operating room. Our adult trauma service takes care of most children older than 5 years of age and the pediatric surgical service takes care of children younger than 5 years of age because of the greater availability of adequate manpower on the adult trauma service.

Pediatric surgeons seem to be much more conservative than other surgeons and believe one should not operate on infants until there is something catastrophic going on. This is reflected in the delay in diagnosis in the one case.

Most of these injuries were diagnosed within the first few hours of injury and surgery was carried out promptly. Only in the two patients with late diagnoses did we have morbidity. Dr Bloch, the seat-belt injury is not an innocuous injury and the seat-belt stripe indicates major deacceleration and high probability of significant injury.

We have seen transection of the vertebral column in association with the seat belt as well as total disruption of all the anterior abdominal muscles. Dr Carrico, the injury that results in major serosal flaps ought to be treated as a through-and-through injury. We also see minor serosal tears and, under these circumstances, generally repair them unless they are associated with major contusion or evidence of devascularization. Dr Miller, we had one late injury. It was an injury that at operation appeared to be a contusion. There was a hemorrhage in a segment of the wall of the intestine, and the patient subsequently developed obstruction and required resection.

In Other AMA Journals

AJDC

Congenital Smooth Muscle Hamartoma: Prevalence, Clinical Findings, and Follow-up in 15 Patients

Alexander Zvulunov, MD; Aryeh Rotem, MD; Paul Merlob, MD; Aryeh Metzker, MD

Congenital smooth muscle hamartoma is a congenital skin lesion characterized by proliferation of bundles of smooth muscle within the reticular dermis. We report on a group of 15 children with this lesion, confirmed by skin biopsy specimen, its prevalence, the occurrence of associated anomalies, and long-term follow-up. To our knowledge, this is the largest group of patients with this lesion described in the literature. The estimated prevalence is about 1:2600 live births with slight male predominance. The lesion is most frequent in the lumbosacral area (67% [10/15]) and a positive pseudo-Darier's sign is present in 80% (12/15) of patients. During the follow-up period of up to 7 years, the lesions enlarged slightly but became less prominent. No malignant transformation was observed. (*AJDC*. 1990;144:782-784).

Reprint requests to Pediatric Dermatology Unit, Beilinson Medical Center, Petah Tiqwa 49 100, Israel (Dr Metzker).

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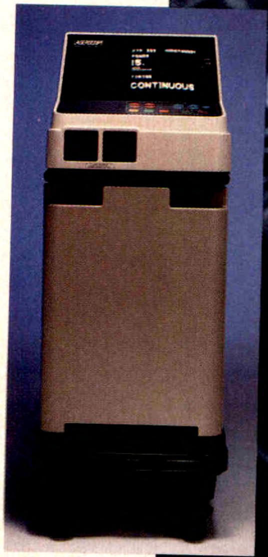

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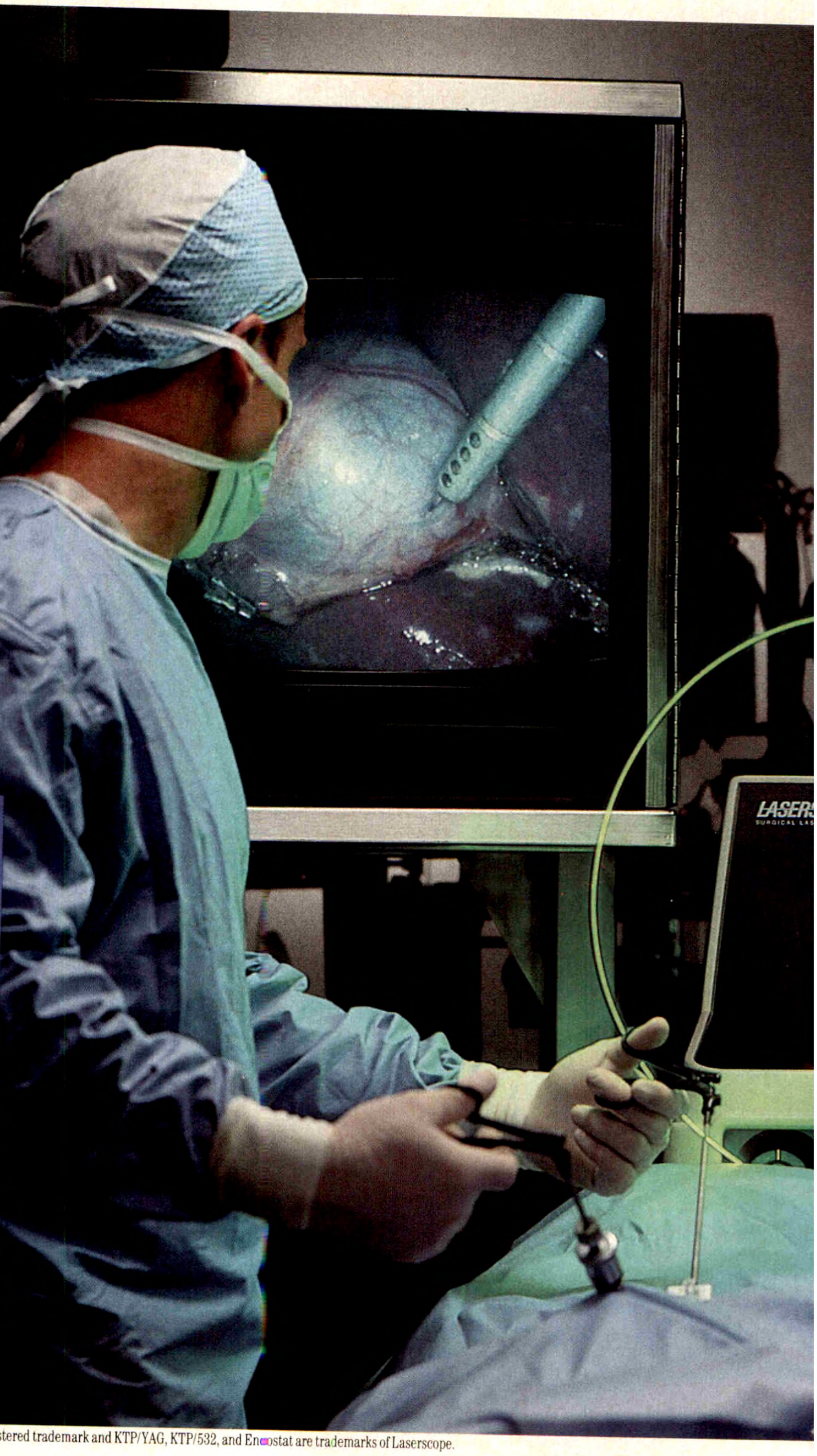

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The Operative Management of Coexisting Thyroid and Parathyroid Disease

Seth D. Strichartz, MD, Armando E. Giuliano, MD

• Three hundred eight patients who underwent operation for hyperparathyroidism were studied. Fifty-two (17%) were identified who had a concomitant thyroid nodule. All 52 underwent parathyroidectomy and thyroid resection in a single operation. Eleven of these patients (21% of those with a thyroid nodule) had differentiated thyroid cancer. One patient with parathyroid hyperplasia developed permanent hypocalcemia. None had permanent vocal cord paralysis and none required tracheostomy. Thorough visual inspection and palpation of the entire thyroid gland should be performed during operations for hyperparathyroidism. Incidentally discovered thyroid nodules should prompt formal lobectomy with frozen section diagnosis; unanticipated thyroid malignancies should then be treated as independent entities. Treating simultaneous hyperparathyroidism and nodular thyroid disease with a single operation can be done safely; it avoids the expense and risk associated with neck reexploration and can detect unsuspected cancers.

(*Arch Surg.* 1990;125:1327-1331)

The unexpected finding of nodular thyroid disease during a neck exploration for hyperparathyroidism (HPT) was first reported in 1954.[1] Since that early report, multiple series have documented an incidence of thyroid abnormalities in patients with primary HPT that ranges from 20% to 60%.[2-5]

The association between HPT and *medullary* thyroid cancer in the multiple endocrine neoplasia (MEN) II syndrome (Sipple's syndrome) is well described and can be understood based on common embryologic origins in the cell lines. However, HPT, due to either a parathyroid adenoma or to hyperplasia, and papillary or follicular thyroid cancer may also coincide.[2-19] Whether the coexistence of these entities is more than a chance association, or simply represents the fortuitous simultaneous discovery of two common diseases, remains a matter of debate.

This association, regardless of cause, leaves the surgeon with the possibility of encountering a second unexpected, potentially serious lesion at the time of parathyroidectomy. Already sensitive to the risk of complications associated with parathyroid exploration, the operating surgeon is often reluctant to pursue a possible thyroid abnormality at the time of initial neck exploration. Thyroid resection in addition to parathyroidectomy with exploration of all four glands may increase the risk of complications. However, since thyroid malignancy may coexist with HPT, the successful diagnosis and treatment of unexpected thyroid abnormalities is essential. Delay in diagnosis could result in an overlooked cancer, of which subsequent therapy could result in greater difficulty during a second neck exploration, more complications, and possibly more recurrences. We examined the experience at UCLA during a recent period with patients found to have coexistent parathyroid and thyroid abnormalities, to determine the effects of simultaneous treatment and to formulate a rational plan of management.

PATIENTS AND METHODS

The computerized records of the Department of Pathology and the UCLA Medical Center from 1976 through 1989 were reviewed. Patients with biochemically and histologically proven HPT and who had thyroid nodules found at operation were identified. Only patients with histologically demonstrated thyroid disease and histologically and biochemically proven HPT are included in this report. Patients with medullary carcinoma, with or without proven multiple endocrine neoplasias, were excluded.

RESULTS

Three hundred eight patients underwent parathyroidectomy for HPT. A subset of 52 patients (17%) were identified who also had gross thyroid abnormalities and histologically confirmed thyroid disease. Forty-three were women and nine were men. The average age of the patients with combined disease was 55 years (women, 57 years; men, 48 years). Thirty-seven patients were identified with parathyroid adenomas and 15 with hyperplasia.

Of the 52 patients, 11 had differentiated thyroid cancer. This represents 21% of those patients with concurrent thyroid abnormalities and 3.6% of all patients undergoing neck exploration for HPT. Of these 11 patients, 10 had parathyroid adenomas and one had hyperplasia. One patient had follicular cancer and the remaining 10 had papillary carcinomas. One of the patients had histologically documented spread to regional lymph nodes at the time of parathyroid exploration and underwent a paratracheal lymph node dissection. Only one of the 11 patients with thyroid cancer had a palpable thyroid nodule preoperatively; the nodule was hypofunctioning on a radioiodine scan. Of the patients with cancer, six denied any history of prior radiation therapy to the head and neck, one had a known history of prior radiotherapy for acne, and the records of four patients did not contain a specific reference to prior radiation exposure.

Three of the cancers were less than 0.5 cm. Two were between 0.5 and 1.0 cm and five were larger than 1.0 cm. The patient with metastases to regional lymph nodes had only microscopic disease, despite serial sectioning of the gland. Two patients had multifocal cancers.

Three of the neck explorations in the group with thyroid cancer were reexplorations. One patient had a prior thyroid

Table 1.—Treatment of Coexisting Thyroid Abnormalities in Patients With Hyperparathyroidism*

	No. of Patients			
	SL	TL	ST	TT
Nodular goiter	3	14	5	0
Nonmedullary carcinoma	0	2	4	5
Follicular adenoma	3	5	1	0
Hashimoto's thyroiditis	3	3	0	1
Chronic thyroiditis	0	1	1	0
Hurthle cell adenoma	0	1	0	0

*SL indicates subtotal lobectomy; TL, thyroid lobectomy; ST, subtotal thyroidectomy; and TT, total thyroidectomy.

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lobectomy for nodular goiter and two were reexplored for recurrent HPT. One of these two previously had a benign follicular adenoma of the thyroid gland discovered at the time of removal of a parathyroid adenoma. It was unclear whether the second patient reexplored for HPT had thyroid disease noted at the previous exploration.

In addition to the 11 patients with thyroid cancer, 22 were found to have nodular goiter, nine had benign thyroid adenomas, seven had Hashimoto's thyroiditis, two had chronic thyroiditis, and one had a Hurthle cell adenoma, as detailed in the tabulation below:

Histologic Diagnosis	**No. of Patients**
Nodular goiter	22
Differentiated cancer	
Papillary	10
Follicular	1
Benign adenoma	9
Hashimoto's thyroiditis	7
Chronic thyroiditis	2
Hurthle cell adenoma	1

The extent of thyroid resection performed was based on the individual surgeon's preference. Twenty-six patients were treated with thyroid lobectomy, 11 with subtotal thyroidectomy, nine with subtotal lobectomy, and six with total thyroidectomy. Of the patients with thyroid cancer, five underwent total thyroidectomy, four underwent subtotal thyroidectomy, and two underwent lobectomy (Table 1).

The most common complication of combined parathyroidectomy and thyroidectomy was transient hypocalcemia. This occurred in 13 patients. Transient hypocalcemia was defined as hypocalcemia requiring supplementation in the immediate postoperative period that could be discontinued subsequently. Permanent hypocalcemia occurred in only one patient. This patient underwent subtotal thyroidectomy for a large nodular goiter, concurrently with a 3.5-gland parathyroidectomy. The patient was hypocalcemic and underwent reimplantation of frozen parathyroid tissue into the forearm 1 year later. No patient with thyroid cancer suffered a complication. Two patients undergoing total thyroidectomy experienced transient hoarseness. No patient experienced permanent vocal cord paralysis. A 75-year-old patient experienced a nonfatal myocardial infarction after excision of a parathyroid adenoma with concomitant thyroid lobectomy for Hashimoto's thyroiditis. Another elderly patient developed transient atrial fibrillation postoperatively but did not suffer hemodynamic compromise. The tabulation below lists the complications of concomitant thyroid and parathyroid resection.

Complications	**No. (%)**
Transient hypocalcemia	13 (25)
Transient hoarseness	2 (4)
Permanent hypocalcemia	1 (2)
Transient arrhythmia	1 (2)
Myocardial infarction (nonfatal)	1 (2)
Permanent hoarseness	0 (0)
Tracheostomy	0 (0)

In all but one patient, the thyroid and parathyroid abnormality were definitively addressed at the same operation. The exception was a 14-year-old patient who underwent completion thyroidectomy several days after undergoing thyroid lobectomy and resection of a parathyroid adenoma; the diagnosis of follicular adenoma initially made by frozen section on the thyroid nodule was subsequently determined to be a follicular variant of papillary carcinoma on permanent hematoxylin-eosin–stained sections. She underwent an uncomplicated total thyroidectomy 3 days later.

COMMENT

During a recent 13-year period at UCLA, 52 patients were identified who had concurrent HPT and nodular thyroid disease. All 52 underwent thyroid resection in addition to parathyroidectomy. Eleven (21%) of the patients with a thyroid nodule had histologically proven papillary or follicular thyroid cancer. Only one had a palpable thyroid nodule preoperatively. One of the 11 had regional lymphatic spread at the time of parathyroidectomy. Of the 52 patients, only one (2%) experienced permanent hypocalcemia after a 3.5-gland parathyroidectomy and subtotal thyroidectomy for a large goiter. No patient had permanent vocal cord paralysis or required tracheostomy.

Table 2.—Incidence in the Literature of Nonmedullary Thyroid Carcinoma in Patients With Hyperparathyroidism (HPT)

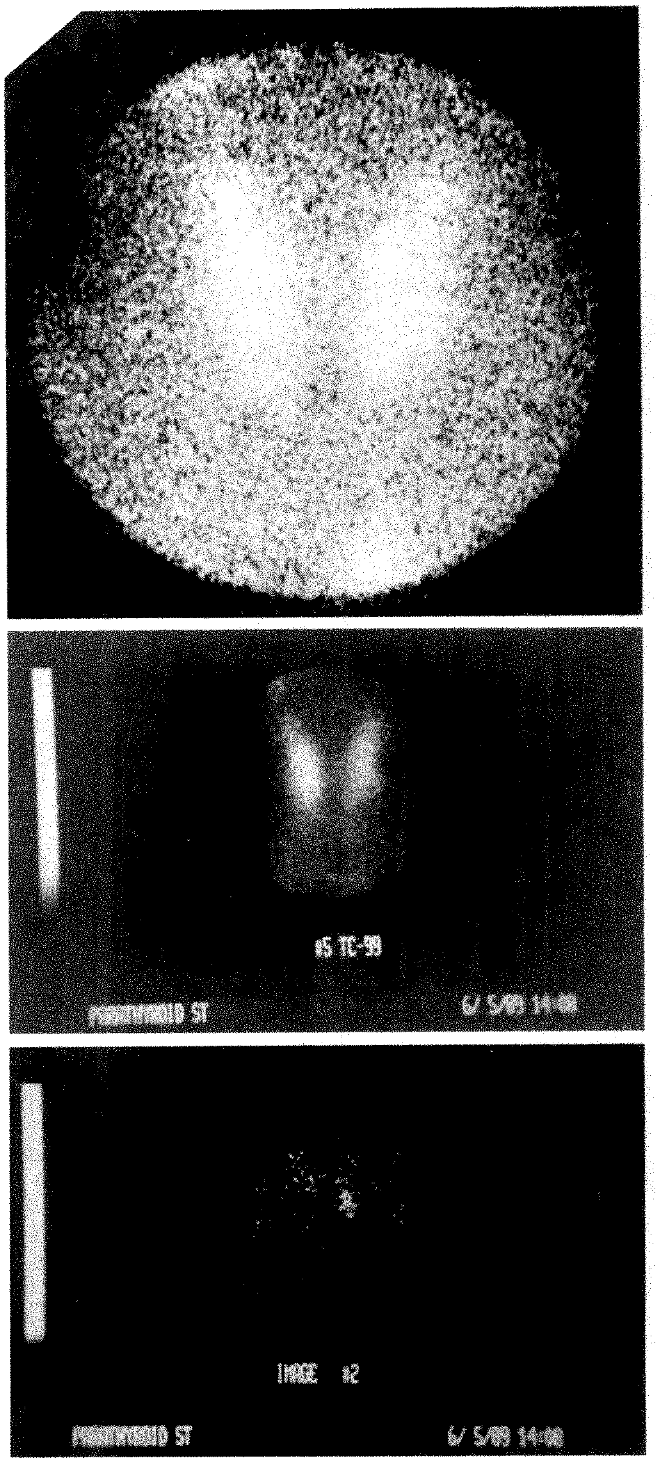
	HPT, No.	**Thyroid Carcinoma, No. (%)**
Ogburn and Black[6]	230	4 (1.7)
Ellenberg et al[7]	93	7 (7.5)
Laing et al[2]	71	3 (4.2)
Kaplan et al[8]	104	5 (4.8)
Trout and Mulder[9]	30	3 (10.0)
Farr et al[10]	100	5 (5.0)
Petro and Hardy[11]	56	5 (8.9)
LiVolsi and Feind[12]	270	29 (10.7)
Prinz et al[13]	89	5 (5.6)
Calcaterra and Paglia[14]	144	11 (7.6)
Nishiyama et al[15]	420	13 (3.1)
Russ et al[16]	74	4 (5.4)
Linos et al[17]	2058	51 (2.5)
Prinz et al[3]	351	15 (4.3)
Lever et al[4]	124	7 (5.6)
Hedman and Tisell[18]	391	19 (4.9)
Van der Schaar and Mulder[5]	30	0 (0)
Diamond et al[19]	46	1 (2.2)
Current study	308	11 (3.6)
Total	**4936**	**198** (4.0)

This study represents a retrospective review of charts from patients whose pathologic specimens contained both thyroid and parathyroid tissue. These patients were cared for by different surgeons at different times. There was no standardized definition of a "thyroid abnormality"; however, the abnormalities identified were all nodules. No protocol as to the extent of resection was used. It follows that there may have been many neck explorations in which thyroid abnormalities were noted but not biopsied or resected. Therefore, the 17% coexistence that we report is likely an underestimate of the true degree of coexistent thyroid disease and HPT.

In 1954, Hellstrom[1] reported a series of 50 parathyroidectomies for HPT. He identified 19 patients with concurrent nodular thyroid disease. Ogburn and Black[6] in 1956 described four patients with primary HPT and nonmedullary thyroid cancer. They reported the finding as a chance association. Subsequent to these early reports, the coexistence of nodular thyroid disease has been documented in up to 60% of patients operated on for HPT.[2-5,7-19] Recently, attention has been turned to the prevalence of differentiated thyroid cancer in patients operated on for HPT. The 3.6% incidence of concurrent thyroid cancer and HPT that we documented is in agreement with the overall prevalence reported in the literature (Table 2).

Whether the association between the two entities represents more than chance remains unclear. Some authors believe that reports of concurrent thyroid and parathyroid disease simply describe the simultaneous occurrence of two common conditions.[19] However, several large autopsy series have shown the prevalence of macroscopic thyroid cancer to be only 0.002% to 0.08% in the general population.[20-22] In 1983, Lever et al[4] compared 124 consecutive parathyroidectomies with age-, sex-, and race-matched autopsy controls. Although they found no statistical difference in the prevalence of total macroscopic thyroid lesions, they did find a greater number of nonmedullary thyroid cancers in the patients with HPT compared with the autopsy controls (5.6% vs 0%, $P<.001$). Similarly, Laing and associates[2] noted the incidence of thyroid cancer in 72 patients operated on for HPT to be 6.0%, compared with 1.0% in 100 consecutive autopsies in their institution. However, the yield for finding thyroid cancer in pathologic specimens is directly proportional to the meticulousness with which a specimen is sectioned.[23] This makes the interpretation of data regarding the prevalence of thyroid cancer in patients with HPT difficult.

In the MEN II syndrome (Sipple's syndrome), in which medullary thyroid cancer and HPT occur together, the association between the thyroid and parathyroid conditions can be explained by a defect in a common neuroendocrine cell line (amine precursor uptake and decarboxylation cells). However, this reasoning does not explain the association between papillary or follicular thyroid cancer and HPT, as these tissues are derived from different cell lines. Since there is no apparent embryologic explanation for the coexistence of the entities, other etiologic factors must be implicated. It has been demonstrated that hypercalcemia has a significant goiterogenic effect in rodents, but this has not been found in humans.[24] Furthermore, no difference in the degree or duration of hypercalcemia was demonstrated in patients with thyroid cancer and HPT compared with patients with HPT without thyroid cancer.[4] Diamond et al[19] documented higher calcium levels in those patients in their series with only HPT compared with patients with both HPT and thyroid disease. Additionally, the proposed mechanism whereby hypercalcemia induces thyroid disease is based on an alleged hypercalcemia-dependent hypercalcitoninemia, but the data regarding elevated calcitonin levels during HPT are conflicting.[25-27]



Thallium-technetium scan of a patient with a right superior parathyroid adenoma and a left-lobe thyroid carcinoma. Top, Thallium image of thyroid and parathyroid glands. Center, Technetium image of thyroid gland. Bottom, Subtraction image interpreted as demonstrating left inferior parathyroid adenoma.

A more popular theory explaining the concurrence of these two diseases implicates prior head and neck irradiation.[15,18,28] It has been demonstrated that prior irradiation confers an increased risk of subsequent papillary thyroid cancer.[23,29,30] There is also evidence suggesting that head and neck irradiation may play a role in the eventual development of primary HPT.[18,31] Prinz et al[28] reported that of the 12 patients with both differentiated thyroid cancer and HPT whom they treated, eight had received prior head and neck irradiation. Russ et al[16] reported that four of 19 patients with HPT and nonmedullary thyroid cancer had a history of irradiation to the head and neck region. However, of 55 of their patients with HPT and no history of radiation, none had a concomitant thyroid cancer. Hedman and Tisell[18] found that 17.5% of patients with HPT who had been irradiated had concurrent thyroid cancer, while only 2.4% of the nonirradiated group did ($P<.001$). Nishiyama et al[15] reported that 50% of their patients with HPT who had been exposed to regional radiation had concurrent cancer of the thyroid, while only 12% of the patients with HPT not exposed to radiation had simultaneous thyroid cancer. Although we found only one patient in our group with concurrent HPT and thyroid cancer who had a history of prior head and neck irradiation, obtaining an accurate history of prior radiotherapy is notoriously difficult. One hundred patients treated with x rays for tuberculous cervical adenitis between 1930 and 1946 were interviewed 30 years later; 36 were unaware of the prior radiation therapy, despite the fact that 11 of them were over 25 years old when they received the x-ray therapy.[32] Without a concerted effort to obtain this history using family member interviews, reviews of all old medical records and discussions with all of a patient's prior physicians, the lack of a prior radiation history is difficult to interpret.

Five of the 11 cancers detected in this study were less than 1.0 cm in diameter. However, all cancers, except in the patient with involved regional lymph nodes, were macroscopic. Thyroid cancers less than 1.0 cm have been deemed "incidental" due to the excellent long-term results achieved with resection. No surgeon, however, would likely advocate leaving in place a macroscopic thyroid cancer identified at a neck exploration, regardless of the tumor's small size. There is no way to know that a patient with an "incidental" thyroid cancer left unresected will enjoy the relatively benign course that one can expect from a patient whose "incidental" cancer is resected. It cannot be disputed that all large cancers were once small.

Based on the accumulated data regarding the occurrence of simultaneous HPT and papillary/follicular thyroid cancer, careful intraoperative palpation and inspection of the entire thyroid gland at the time of parathyroid resection is recommended. While in our series the overall incidence of thyroid cancer in patients explored for HPT was only 3.6%, those patients explored for HPT who had a thyroid nodule had a 21% chance of concomitant thyroid carcinoma. The absence of a palpable thyroid abnormality preoperatively is inadequate to rule out the presence of thyroid disease. Only one of the patients with thyroid cancer and HPT in this series had a thyroid nodule detected preoperatively. Prinz et al[3] noted that in only 37% of patients with concurrent disease was a thyroid abnormality appreciated preoperatively. Van der Schaar and Mulder[5] found that preoperative palpation missed 14 of 21 lesions found intraoperatively. They concluded that all patients with HPT should undergo thyroid scintiscan preoperatively. Calcaterra and Paglia[14] also concluded that in addition to careful intraoperative palpation of the thyroid, "a radioactive iodine scan and an ultrasound study of the gland may be advisable." Although we do not believe that all patients with HPT require preoperative nuclear scans, we stress the importance of intraoperative inspection and palpation of the *entire* thyroid. We do not routinely obtain preoperative parathyroid imaging studies for a first neck exploration. It has been shown that at least 95% of parathyroid tumors can successfully be localized by an experienced surgeon at a first exploration without these studies.[33] The thallium-technetium subtraction scan may be helpful in examining both the thyroid and parathyroid glands; however, most reports suggest that this scan is only 75% accurate.[34] Furthermore, in patients with thyroid nodules, the rate of false-positive scans for parathyroid abnormalities is increased.[35] The figure shows a thallium-technetium scan in which the left lower pole abnormality was interpreted to be a parathyroid adenoma. At operation, however, this proved to be a papillary carcinoma with a right upper lobe parathyroid adenoma.

A solitary thyroid nodule must be examined at the time of parathyroidectomy. Thyroid cancer discovered at the time of neck exploration for HPT deserves definitive treatment at the same operation. The increased risk of reoperative thyroid surgery is well documented and is worth avoiding.[36] Linos et al[17] reported that the risk of hypocalcemia with concomitant thyroid and parathyroid resection is greater than with parathyroid resection alone. However, the 52 patients in the current study with thyroid and parathyroid abnormalities were treated with simultaneous resections with no permanent recurrent laryngeal nerve injury and only one case of permanent hypocalcemia. The patient with permanent hypoparathyroidism had a large goiter and parathyroid hyperplasia and underwent a difficult subtotal thyroidectomy and a 3.5-gland parathyroidectomy. No patient with cancer suffered a complication. Whether the incidence of serious complications would have been higher with a greater number of total thyroidectomies is only speculative.

We believe that an incidentally discovered thyroid nodule should prompt formal lobectomy with a frozen-section diagnosis of the nodule. A differentiated thyroid cancer discovered in this manner should be treated as an independent entity with whatever degree of thyroid resection the surgeon can safely perform for definitive surgical treatment. However, the presence of a small or moderate-sized multinodular goiter without a dominant nodule, and in a patient without a history of regional radiation therapy, is, in and of itself, not justification for thyroid resection.

While some authors suggest that the risk of concomitant thyroid and parathyroid resection may be higher than with either operation performed alone, our experience suggests that a single operation for both can be performed safely. Performing a definitive thyroid resection at the time of parathyroidectomy avoids a possible neck reexploration with its attendant increased expense and morbidity.[36]

In the current series of 11 patients with both HPT and differentiated thyroid cancer, five were treated with total thyroidectomy and six were treated with subtotal thyroidectomy without complications. Overall, 52 patients with nodular thyroid disease and HPT underwent combined thyroid and parathyroid resections; only one experienced permanent hypocalcemia. Careful inspection and palpation of the entire thyroid gland with diagnosis and definitive treatment of a malignancy should be performed at the time of parathyroidectomy.

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Discussion

ORLO H. CLARK, MD, San Francisco, Calif: How should the surgeon manage thyroid abnormalities in patients with HPT? Ogburn and Black[6] found four cases of papillary or follicular cancer among 299 patients treated surgically for HPT. Ellenberg and colleagues[7] found seven cases of nonmedullary thyroid cancer among the first 93 patients with HPT operated on at the University of California, San Francisco. LiVolsi and Feind[12] found 31 thyroid cancers (11.4%) among 272 patients with HPT. Linos et al[17] reported that 51 (2.5%) of 2058 patients treated surgically at the Mayo Clinic had thyroid cancer. Combining 10 series including the above cases, 120 (3.8%) of 3200 patients with HPT had thyroid cancer. These series underestimate the actual frequency of cancer since not all patients had their thyroid glands removed.

It is unknown whether there is a higher frequency of thyroid cancer in patients with HPT or if there is a higher frequency of HPT in patients with thyroid disorders. Stoffer et al[37] reported that "hyperparathyroidism was 10 times more frequent in patients with thyroid disorders, especially nodular goiter, than expected in the general medical population." The incidence of thyroid disease in patients with HPT was 39%. When thyroid abnormality is searched for in patients with HPT either at autopsy or by various scanning techniques, up to 70% of patients with HPT have associated thyroid disorders. Using preoperative ultrasound and/or computed tomographic scanning in patients with HPT, we documented thyroid abnormalities in 43% of the patients. I ignored most of these coexistent thyroid abnormalities during the parathyroid operations.

Certain situations increase the chance of thyroid cancer. Patients who have been exposed to low-dose therapeutic radiation, especially as children, have a higher incidence of benign and malignant thyroid neoplasms, as well as HPT. Patients with MEN type 2A have HPT and medullary thyroid cancer. Of interest is that the oncogene associated with MEN 2A is on the same region of chromosome 10 q11-q12 as is the human papillary thyroid cancer oncogene.[38] Since calcium is a goitrogen, patients with HPT could have more thyroid nodules.

When should a surgeon remove a thyroid nodule or thyroid gland in patients with HPT? Certainly, patients with a history of exposure to low-dose therapeutic radiation require thyroidectomy because 40% of these patients will have thyroid cancer when a thyroid nodule is present in the thyroid gland. Patients with familial thyroid cancer or with MEN 2A who have medullary thyroid cancer and HPT warrant thyroidectomy. Patients with thyroid nodules over 1.5 cm, especially if solitary or hard or associated with lymph node metastases, should be removed.

One could also perform percutaneous aspiration biopsy cytologic tests prior to thyroidectomy under ultrasound guidance to document whether thyroid cancer is present. Symptomatic thyroid nodules should also be removed.

It may be that many of these thyroid cancers remained indolent and were only discovered because of the parathyroid operation. A good control group would be patients having thyroid tissue removed during operations for secondary HPT or Graves' disease.

What were the size of the thyroid nodules? What were the reasons for not doing total thyroidectomy in patients with thyroid cancer? Is there a different surgical approach for patients with thyroid nodules, HPT, or both? How would Dr Giuliano manage a patient with parathyroid hyperplasia and nonmedullary thyroid carcinoma?

THEODORE X. O'CONNELL, MD, Los Angeles, Calif: I would take a different tack than the authors. I think their data tell us not to examine the glands too closely. Fully 80% of their lesions are benign and do not need any treatment at all. It looks like they were overtreated.

Patients with Hashimoto's thyroiditis and nodular goiter were getting subtotal thyroidectomy, which is unnecessary treatment and exposes the patient to the risk of laryngeal nerve damage and HPT.

Approximately 20% of the patients did have carcinomas. How many of these lesions were papillary carcinomas less than 1 cm in diameter that would be considered to be clinically insignificant and not need treatment at all?

H. EARL GORDON, MD, Los Angeles: Any thyroid lesion unexpectedly encountered at the time of a parathyroid exploration should be appropriately treated at the same operation. I would limit this resection to those lesions for which a thyroidectomy is commonly indicated and not the minor nodules that are frequently encountered.

However, if you are dealing with a cancer or a sizable nodule of undetermined origin, these should be handled at the same operation. The risk is certainly going to be less in a combined procedure than to defer the thyroid resection to a second operation at some future time.

The authors confined their pathological findings to nodular lesions. It is also possible for HPT and Graves' disease to be coexistent as well. I would like to carry this one step further. If one is doing a thyroidectomy, one should be equally meticulous in exploring the neck for any parathyroid abnormality that might unexpectedly be encountered. Any patient who is having a thyroidectomy should have a preoperative calcium. While performing a thyroidectomy, I have encountered parathyroid glands two or three times enlarged, raising the possibility of hyperplasia. A preoperative serum calcium measurement is very helpful in such cases.

In patients who have parathyroid hyperplasia and thyroid cancer, the risk of recurrent nerve injury and hypocalcemia can be significant and demands meticulous surgical technique.

DR GIULIANO: Dr Clark, the incidence of thyroid abnormalities in patients with HPT is higher than in the normal population. Clinical and autopsy studies show that patients with HPT have a higher incidence of carcinoma of the thyroid. When operating for HPT, if thyroid abnormality is found, it should be addressed. Most of the abnormalities are benign, but 20% of the palpable nodules were malignant. If a patient had a history of radiation therapy to the head or neck, I think the thyroid gland should be examined, and if a thyroid nodule is found, the patient should be treated with total thyroidectomy. In a multiple goiter, a nodule that is not firm or irregular with no abnormal lymph nodes can be left untreated.

A patient with primary HPT who has a thyroid nodule has carcinoma 20% of the time. Thyroid and parathyroid abnormalities can both be treated at the same operation with a very low incidence of complications. The Mayo Clinic reports 20% permanent hypoparathyroidism, but we had only one. The low incidence of complications justifies treating both lesions at the same time. Some patients will have benign nodules resected that could have been left in place, but you do not know that until you remove them and make the diagnosis.

Dr O'Connell asked if these are insignificant cancers and are better left alone. Maybe, but once they are found, it behooves us to treat the cancer. Large cancers were once small and leaving small ones untreated makes no sense to me. A thyroid nodule found at parathyroidectomy is removed by formal lobectomy and a frozen section is obtained. If this is malignant, proceed with definitive therapy, which in my hands is total thyroidectomy.

Seventeen percent of patients with HPT have a thyroid nodule and 20% of those are malignant. The diagnosis and treatment of these nodules can be done at a single operation with very few long-term complications.

The Efficacy of Central Venous and Pulmonary Artery Catheters and Therapy Based Upon Them in Reducing Mortality and Morbidity

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• The purpose of this study was to (1) evaluate the relative cost effectiveness of the central venous pressure and flow-directed pulmonary artery catheters used to maintain normal hemodynamic values as therapeutic goals in the control groups vs supranormal values empirically observed in critically ill postoperative survivors in the protocol groups, and (2) to evaluate tissue perfusion and oxygenation in relationship to organ failure and mortality. In two prospective clinical trials there were no significant differences in outcome between the central venous pressure and pulmonary artery control groups that used normal values as therapeutic goals. However, there were marked and significant reductions in morbidity and mortality of the protocol groups using the supranormal cardiac index, oxygen delivery, and oxygen consumption values as goals. The cumulative oxygen debt was less and organ failures were fewer and less severe in the protocol groups than in the control groups.

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The balloon tip, flow-directed, Swan-Ganz pulmonary artery (PA) catheter has allowed cardiac catheterization to be performed at the bedside of the critically ill patient.[1-3] The concept that catheters can be placed and various physiologic measurements made in patients with shock and critical illness is more than half a century old.[4] However, therapeutic plans based on physiologic measurements that are tested prospectively for efficacy has been slow in coming. The idea that a patient may be too ill or in a condition that is too unstable for meaningful measurements to be made was dispelled by Cournand et al,[5] who demonstrated reduced cardiac output in patients in traumatic shock with hypovolemia.

Experimental and clinical studies have shown the importance of flow and oxygen transport as measures of overall circulatory function and tissue perfusion in several important conditions: (1) characterization of the various types of shock[3,5,6-11]; (2) description of the sequential patterns of evolving shock syndromes[6,7,10]; (3) differentiation of the circulatory patterns of surviving and nonsurviving patients[6,7,10,11]; (4) prediction of outcome[7,11,12]; (5) evaluation of the relative effectiveness of various types of alternative therapies[3,9,13-16]; and (6) prospective testing of these therapeutic approaches in clinical trials.[7] These studies were descriptive and empirical; they were not based on the popular preconceptions of shock or its current therapy, and essentially they did not require any important assumptions.

The acquisition of monitored data per se does not directly affect outcome unless these data lead to changes in therapy. To evaluate the potential cost-effectiveness of a monitored system, it is therefore necessary to define specific therapeutic goals for the important variables being monitored. As in other laboratory analyses, the normal range of variables must be defined and the optimal range of values must be specified in conditions where they are different from the normative standards.

The aim of this ongoing study is to follow up a previously reported series[7] with additional observations: (1) evaluation of high-risk criteria for preoperative patients in general surgical units; (2) the effectiveness of monitoring at various times in the postoperative period vs preoperative or early prophylactic monitoring; (3) the use of the pattern of oxygen consumption ($\dot{V}O_2$) variables to estimate oxygen debt; and (4) the efficacy of supranormal hemodynamic and oxygen transport values as treatment goals to improve outcome. The tested hypothesis was that early aggressive prophylactic therapy that forces the high-risk patient into the survivor pattern after surgery improves outcome. The corollary hypothesis was that prevention or early correction of the oxygen debt estimated from oxygen transport variables reduces organ failure and death.

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MATERIALS AND METHODS

Reference Series to Define High-Risk Criteria

Twenty-five years ago, we began routinely selecting the most severely ill patient available for invasive monitoring; this judgment was made on the basis of his or her clinical status. In essence, we monitored the patient considered to have the highest risk of dying after surgery. Subsequently, we evaluated the risk factors identified before surgery from January 1975 to December 1988 in terms of patient outcome (Table 1).

Definition of Therapeutic Goals

Normal values were the therapeutic goals in the control groups as well as in the control series between the first and second trials and the poststudy control period. By contrast, the therapeutic goals in the protocol group were supranormal values for cardiac index (CI) (4.5 L/min/m^2), oxygen delivery (Do_2) (>600 mL/min/m^2), and oxygen consumption ($\dot{V}\text{o}_2$) (>170 mL/min/m^2) previously defined empirically from the median values of patients surviving critical surgical illnesses.[6,12] These goals were given high priority in the treatment of protocol patients.

First Prospective Clinical Trial

The first prospective trial consisted of 276 operations performed from January 1978 to June 1980 on 252 high-risk surgical patients requiring PA catheters. The patients were allocated by services to a control group with normal values as therapeutic goals and a protocol group with supranormal values as goals.

Control Period Between the First and Second Clinical Trials

Between the first and second clinical trials another control period was undertaken to determine if similarly high mortality rates for high-risk surgical patients occurred after the first series, ie, from June 1980 to May 1983.

Second Prospective Clinical Trial

The second prospective trial was undertaken from May 1983 to May 1984 to provide a more rigorous trial in which patients were strictly randomized before surgery by opening a sealed opaque envelope prepared by an outside person from a random number table; patients were then followed up during and after surgery according to their designated allocation to central venous pressure (CVP-control), PA-control, or PA-protocol groups. There were 146 high-risk patients who met one or more of the high-risk criteria before surgery and were offered the opportunity to participate in a strictly randomized trial. Of these, 45 patients were not randomized because, in the opinions of their resident or staff physicians, they were not considered ill enough to justify the 67% likelihood of invasive monitoring. Ten other patients were taken to the operating room directly as emergencies and three patients' operations were canceled; the remaining 88 patients were strictly randomized before surgery to one of three monitoring/treatment groups: (1) CVP-control group, ie, CVP with treatment based on the normal values provided by the CVP catheter as therapeutic goals; (2) PA-control group, ie, PA catheter with treatment based on the normal values provided by the PA catheter as

Table 1.—Criteria for High-Risk Patients and Their Distribution to Therapeutic Groups

High-Risk Criteria	Reference Series	No. of Patients With High-Risk Criterion*			
		First Series		Second Series	
		Control	Protocol	Control	Protocol
Previous severe cardiorespiratory illness (eg, acute myocardial infarction, chronic obstructive pulmonary disease)	110 (20)	13 (39)	18 (0)	12 (8)	4 (6)
Extensive ablative surgery planned for carcinoma (eg, esophagectomy and total gastrectomy; prolonged surgery [>8 h])	86 (20)	29 (34)	9 (11)	6 (0)	8 (12)
Severe multiple trauma (eg, more than three organs or two systems or opening two body cavities)	29 (28)	16 (25)	7 (14)	0	1 (0)
Massive acute blood loss (>8 U); blood volume <1.5 L/m²; hematocrit 0.20	26 (27)	5 (20)	9 (11)	1 (100)	1 (0)
Age >70 y and evidence of limited physiologic reserve of one or more vital organs	145 (35)	36 (36)	26 (35)	4 (25)	5 (0)
Shock: mean arterial pressure <60 mm Hg; central venous pressure <15 cm of water; urinary output <20 mL/h	9 (11)	4 (25)	2 (50)	0	1 (0)
Septicemia: positive blood culture or septic focus; white blood cell count >13 000; spiking fever to 38.3°C for 48 h	40 (47)	8 (37)	3 (33)	3 (67)	1 (0)
Septic shock: same as above with hemodynamic instability	26 (69)	9 (78)	3 (33)	0	0
Respiratory failure: Pao_2 <60 mm Hg on fraction of inspired oxygen >0.4; intrapulmonary shunt fraction >30%; mechanical ventilation needed >48 h	11 (73)	7 (71)	2 (50)	0	0
Acute abdominal catastrophe with hemodynamic instability (eg, pancreatitis, gangrenous bowel, peritonitis, perforated viscus, gastrointestinal bleeding)	246 (36)	56 (32)	49 (24)	18 (55)	17 (0)
Acute renal failure: serum urea nitrogen >17.9 mmol/L of urea; creatinine >265 μmol/L	10 (60)	1 (33)	1 (100)	1 (100)	0
Late-state vascular disease involving aortic disease	47 (28)	4 (25)	2 (0)	5 (40)	6 (0)
Severe nutritional problems: weight loss >10 kg; plasma albumin concentration <30 g/L; osmolality <280 mmol/L	8 (25)	0	0	1 (100)	0
Acute hepatic failure: bilirubin <51 μmol/L; plasma albumin concentration <30 g/L; lactic dehydrogenase >200 U; alkaline phosphatase >100 U/L; ammonia >70 μmol/L	6 (100)	4 (100)	0	0	0
Central nervous system failure, coma	4 (75)	3 (67)	1 (100)	0	0
Total deaths/risk criterion (mortality)	**270/803** (34)	**75/197** (38)	**30/132** (23)	**19/51** (37)	**1/44** (3)

*The numbers in parentheses indicate the percent of mortality when the criterion occurred.

therapeutic goals; and (3) PA-protocol group, ie, PA catheter with treatment based on the supranormal optimal values determined empirically from survivor patterns as therapeutic goals.

Fluid therapy and fluid losses were measured and recorded during surgery and in the first 48 hours after surgery in the control and protocol patients.

Poststudy Control Period

At the end of the second series, a policy limiting PA catheter use to patients who had major clinical circulatory problems was instituted because of cost factors. The prophylactic use of PA catheters was only permitted for advanced circulatory problems, not for high-risk general surgical patients without existing circulatory problems. This policy was begun before we were able to review the charts and analyze our data. High-risk patients were followed up from May 1984 to May 1985.

Physiologic Methods

Pulmonary artery catheters were placed percutaneously in study patients along with systemic arterial catheters to measure hemodynamic values and oxygen transport variables by previously described methods.[6,7,12] The measurements of data sets were taken within a 1- to 2-minute period to calculate oxygen transport and other derived variables for each of the various intervals; 2186 sets of data were obtained in 252 patients from the first clinical trial and 984 sets from the second trial. Similarly, 239 patients were observed in a control period between the first and second series and 160 patients were observed in the poststudy control period. Altogether, more than 700 000 measured and derived values were analyzed in this study.

Therapeutic Approach

The priorities of the control groups (CVP and PA) were normal values that were the standard of practice in our institution; supranormal values of survivors were used for the protocol group. All groups were given essentially the same types of therapy: whole blood, packed red blood cells, colloids, crystalloids, inotropic agents, vasodilators, and vasopressors. The difference was that the therapeutic goals in the protocol group required sufficient quantities of fluids (principally colloids) and inotropic agents (principally dobutamine) to attain the therapeutic goals.

Statistical Methods

Morbidity and mortality rates were analyzed by χ^2 analysis with Yates' correction for small cell size. Hemodynamic data within groups and between groups were analyzed with paired and unpaired Student's *t* tests and analysis of variance (ANOVA) with Newman-Keuls Test for significance of individual comparisons.

RESULTS

Evaluation of High-Risk Criteria

Table 1 lists high-risk factors and mortality rates in a reference population of 708 consecutively monitored patients and in the control and protocol groups of the first and second prospective clinical trials. The mortality associated with each high-risk criterion in the reference group was similar to that in the control series but was markedly reduced in the protocol groups of both trials.

Outcome Data of the First Clinical Trial

The data of the first clinical trial were previously presented in part[7] and are briefly summarized here for purposes of comparison. Of 151 control patients undergoing 168 operations, 57 died (38%); of 101 protocol patients undergoing 108 operations, 21 died (21%). Sufficient numbers were acquired to stratify patients into the following categories: (1) those with normal preoperative CIs; (2) those with preoperative hyperdynamic patterns from sepsis, trauma, stress, and late-stage cirrhosis; and (3) those with low preoperative CIs from hemorrhage, cardiac problems, and old age. In the series as a whole and in each category in which there were adequate numbers, the protocol patients had higher CIs, $\dot{D}O_2$, and $\dot{V}O_2$ relative to their own preoperative values and relative to the corresponding control patients. However, 31% of these patients entered the study late in their postoperative course; we observed that these patients did not do as well as those whose monitoring began before surgery.

Table 2.—Intraoperative and Early Postoperative Fluid Management*

	CVP-Control	PA-Control	PA-Protocol
Intraoperative Fluid Management, mean ± SD			
Fluid intake, mL			
Crystalloids	3974 ± 4071	3611 ± 3031	3207 ± 1258
Colloids	855 ± 1706	810 ± 897	1072 ± 541
Blood, packed cells	803 ± 1572	828 ± 1659	605 ± 534
Estimated losses, mL			
Blood loss	1255 ± 2012	1162 ± 2737	929 ± 524
Urine output	991 ± 722	743 ± 663	732 ± 819
Fluid loss	2038 ± 1416	1896 ± 1421	1387 ± 1160
Balance, mL	+1348 ± 4590	+1448 ± 1587	+1836 ± 1916
Operative time, h	4.2 ± 2.4	4.1 ± 2.7	3.9 ± 1.6
Fluid Management First 48 Hours After Surgery, mean ± SD			
Fluid intake, mL/48 h			
Crystalloids	7581 ± 2030	5980 ± 1751	6474 ± 1888
Colloids	719 ± 826	781 ± 937	1932 ± 1837*†
Blood, packed cells	261 ± 386	333 ± 443	345 ± 675
Fluid losses, mL/48 h			
Urine output	5119 ± 2061	4383 ± 2425	5887 ± 1833
Other	1056 ± 958	1060 ± 938	1849 ± 1606
Balance, operative and postoperative, mL	+3734 ± 2226	+3099 ± 2741	+2851 ± 2954

*CVP indicates central venous pressure; PA, pulmonary artery.

†$P<.05$ for PA-Protocol vs CVP and PA-Control by unpaired Student's *t* test.

Control Period Between the First and Second Clinical Trials

The control period between the first and second clinical trials documented the persistence of a high (28%) mortality rate for the high-risk surgical patients. Thus, there was only a minimal insignificant after-effect from the first study.

Outcome Data of the Prospective Randomized Trial

There were no significant differences in outcome data between the CVP-control and PA-control groups in the randomized series. However, the PA-protocol group had markedly reduced mortality (4% vs 33%; $P<.02$), number of ventilator days (2.3 ± 3.4 days; $P<.05$), number of intensive care unit days (10.2 ± 1.6 vs 15.8 ± 3.1 days; $P<.05$), and hospital charges ($27 665 vs $37 335). The charges were about 25% less than those for the PA-control group and about 50% less than these for control patients calculated per survivor.

Table 2 lists the fluid intake and estimated losses during the intraoperative period and during the first 48 hours after surgery for each of the three groups. There were no significant differences between the groups except that about twice as much colloids (3 L) were administered to the PA-protocol group during and after surgery. We were able to achieve the supranormal goals with fluids alone in 19 (68%) of 28 patients. Dobutamine was used to attain these goals in 7 (25%) of 28 patients because of its capacity to improve oxygen transport[17]; nitroprusside was used in two patients (7%).

Organ Failure and Other Complications

The number and types of organ failure are shown for each group in Table 3. Only one vital organ failure occurred in the protocol group, while the control groups had significantly

Table 3.—Organ Complications and Failures*

	No. of Complications			
	Nonrandomized Series (n=45)	**CVP-Control (n=30)**	**PA-Control (n=30)**	**PA-Protocol (n=28)**
Postoperative vital organ failure				
Respiratory failure	11	7	9	1
Renal failure	10	7	7	...
Sepsis and septic shock	11	6	9	...
Acute myocardial infarction/failure	6	...	2	...
Hepatic failure	2	2	2	...
Disseminated intravascular coagulation	2	...	2	...
Total failures	**42**	**22**	**31**	**1**
Nonvital organ complications				
Pulmonary edema	2	...	3	2
Pleural effusion	2	2	3	3
Wound infection	2	2	2	1
Evisceration	...	1	...	...
Intra-abdominal abscess	1	1	...	...
Postoperative hemorrhage	1	1	...	1
Pancreatitis	...	1	...	1
Gastric outlet obstruction	...	...	...	1
Urinary tract infection	...	1	...	1
Cerebral infarct	1	...	...	...
Total complications	**9**	**9**	**8**	**10**

*CVP indicates central venous pressure; PA, pulmonary artery.

more organ failures. The number and types of non–organ-failure complications are shown for each group in Table 3. There were no appreciable differences between any of the groups, including the protocol group. This indicates that the protocol group was as susceptible to the usual non–organ-failure complications after surgery as the control groups. There was no evidence that these technical surgical complications are not directly related to tissue perfusion.

Poststudy Control Period

In the poststudy control period, the hospital mortality of the high-risk patients returned to 25% and there were six more PA catheters placed during the postoperative periods than during the preceding year.

Efficacy of Starting Invasive Monitoring After Surgery

Of the 490 control patients from the two clinical trials and the two control periods in which monitoring was started after surgery, 142 died (29%); this rate was similar to the 30% mortality (32/107) of the preoperatively monitored PA-control patients. By contrast, the mortality rate of the protocol patients from the two trials whose monitoring was started before surgery (14% and 4%) was significantly less than that of the control patients whose monitoring was started after surgery (32%; $P<.05$) as well as that of all control patients whose monitoring was begun before surgery (30%; $P<.01$) or after surgery (29%; $P<.05$). The monitoring was started a mean (±SD) of 2473±418 minutes after surgery for nonsurvivors and 1428±206 minutes for survivors.

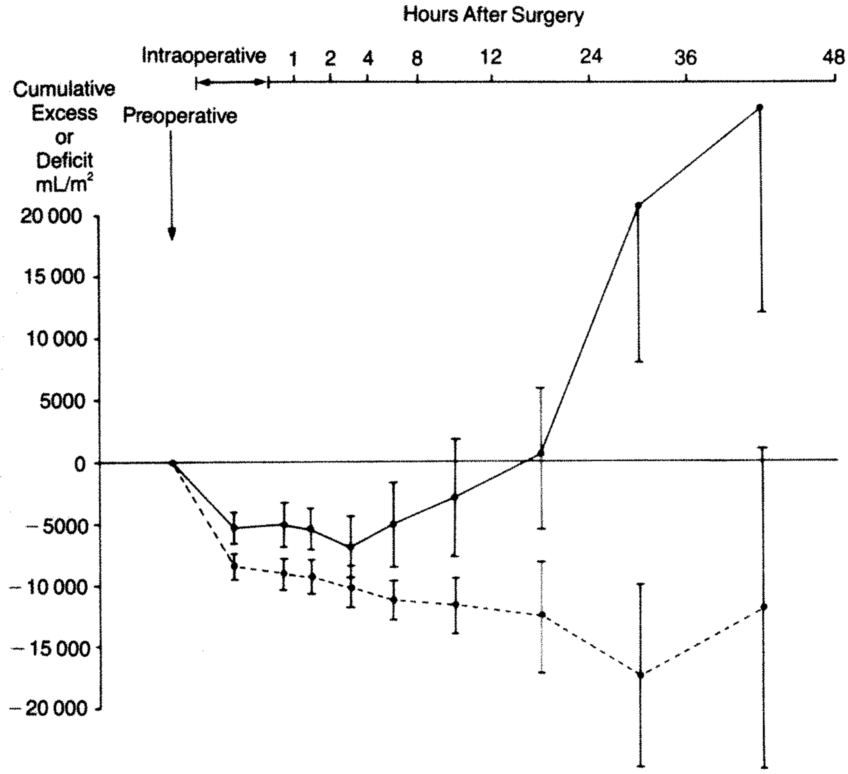
Calculated Oxygen Debt

The $\dot{V}O_2$ needed was estimated from the preoperative baseline $\dot{V}O_2$ values corrected for temperature and for the effect of anesthesia by a previously described method.[17-19] The oxygen debt or excess was calculated as follows: the estimated $\dot{V}O_2$ needed minus the actual $\dot{V}O_2$. The net cumulative oxygen debt was calculated as follows: (estimated $\dot{V}O_2$ needed minus the actual $\dot{V}O_2$) multiplied by time. The sequential pattern of oxygen deficit or excess for the control and protocol patients was computed for the second clinical trial (Figure). The protocol patients had less oxygen debt and this was corrected by about 12 hours after surgery, while the control patients continued to accumulate more oxygen debt for 36 hours after surgery despite their normal blood pressure, CIs, blood gas levels, and urine output.

COMMENT

Controversies about the PA catheter have usually centered on its indications. However, the real issue is not obtaining measurements, but rather the therapeutic use of these measurements. Therefore, it is necessary to separate the measurements obtained by each of the catheters from the uses made of these measurements. Obviously, the measurements per se will not affect outcome, if therapy is not modified because of them. To resolve this issue, we compared the measurements with CVP and PA catheters in relationship to the therapeutic use made of them. When the therapeutic aim was to obtain normal circulatory values, no advantage of the PA catheter was demonstrated. However, when the therapeutic aim was to attain the supranormal (optimal) values, PA catheters significantly reduced mortality and morbidity.

Generally, measurements are made to document an abnormality, which is then corrected by appropriate therapy. Conventional wisdom is to relate cardiac output (or index) values to pulmonary capillary wedge pressures according to the Starling myocardiac performance curve. Using CI values less than 2 L/min/m² to indicate hypoperfusion and wedge pressures greater than 18 mm Hg to indicate fluid overload,



Net cumulative oxygen debt (below 0 line) or excess (above 0 line) for protocol (solid line) and control (dashed line) patients during surgery and at intervals in the early postoperative period. Note that protocol patients had smaller oxygen debts in shorter postoperative periods than control patients.

Forrester et al[3] provided a standardized therapeutic approach based on the four quadrants defined by these two values. This monitoring paradigm has become widely accepted, especially for cardiac patients.

The observation that surgical and accidental trauma, sepsis, stress, and cirrhosis lead to increased flow and oxygen transport, although well documented, is contrary to the traditional wisdom that equates hypotensive shock with low flow. However, it is well documented that survivors have higher flow and greater oxygen consumption than those who died.[11-13] The tested hypothesis was that if early prophylactic therapy brings the patient into the survivor pattern, there will be improvement in mortality and morbidity (Table 1). The basic physiologic mechanism underlying the nonsurvivor pattern was that postoperative circulatory problems result from inadequate (not necessarily low) flow and inadequate (not necessarily low) oxygen transport that produces tissue hypoxia. This can be evaluated as the deficit of oxygen uptake calculated from the difference between the patient's estimated $\dot{V}O_2$ need and the actual measured $\dot{V}O_2$. The evidence of the present study suggests that the amount of estimated oxygen deficit is correlated with death and organ failure. The corollary hypothesis is that if the oxygen debt is prevented, or minimized, and promptly corrected, there will be reduced mortality and morbidity. This was demonstrated in the prospective randomized controlled study (Figure).

We realize that most surgical patients do rather well; overall mortalities of less than 2% in major surgery are usually considered acceptable in most hospitals. Hence, most surgeons are unwilling to depart from their well-organized routines until it is obvious that something has seriously gone wrong. By this time, lethal postoperative complications may already have begun, and it is too late for early, much less prophylactic, therapy. Preoperative identification of high-risk patients and the use of prophylactic monitoring to optimize circulatory function generally have not been accepted. Moreover, the concept has been only slowly appreciated that the high-risk patient could be identified before surgery by clinical criteria and that the majority of surgical deaths and organ failures could be prevented by prophylactic therapy that augmented compensatory responses to tissue hypoxia.

Of considerable interest was the group of 45 patients who met the entrance requirements of the study but were not randomized into the study. The attending surgeons or their chief residents did not want the patients to be included in the study largely because they felt they were not sick enough and did not need monitoring. This group had the highest mortality (38%) and the highest morbidity. Ironically, 60% of these patients ultimately had a PA catheter placed after surgery by those who thought they did not need it. Unfortunately, when the PA catheter was placed, usually after onset of a lethal complication, it did not improve the group mortality. The obvious conclusion is that it is much easier to prevent circulatory problems than it is to treat them after they have become clinically established.

We found empirically that the optimal supranormal goals were much easier to obtain with colloids than crystalloids. This may be contrary to conventional surgical traditions, but it is supported by prospective, random-order, cross-over trials.[14-16]

Finally, immediately after the randomized portion of the study was completed but before we could analyze the data, a departmental decision was made not to place PA catheters before surgery but to wait until the patient had circulatory problems. During this period, the mortality of high-risk patients returned to 25%. Ironically, there was no saving in the number of PA catheters used during that year-long trial. We conclude that the effectiveness of the PA catheter in postoperative patients is seen when it is used prophylactically to prevent organ failure and death from inadequate tissue oxygenation by optimizing cardiac output and oxygen transport variables.

The PA catheter is not more effective than the CVP catheter when cardiac output and intravascular pressures are measured in an uncoordinated manner or when normal values are used as therapeutic goals. The data support the hypothesis that the increased CI and $\dot{D}O_2$ are compensations to the primary physiologic problem of uneven flow, inadequate perfusion, and inadequate tissue oxygenation. Inadequate perfusion can be prevented or corrected by early aggressive therapy directed at attaining supranormal goals empirically defined by survivors. The data also support a second correlative hypothesis that the tissue perfusion deficit can be evaluated as an oxygen debt in the early postoperative period estimated from the net cumulative $\dot{V}O_2$ deficit or excess. The amount and duration of oxygen debt is related to vital organ failure and death. When the $\dot{V}O_2$ deficit is prevented or corrected by early aggressive therapy, marked improvement in outcome occurs.

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Discussion

JAMES W. HOLCROFT, MD, Sacramento, Calif: Optimum hemodynamic values for treating the critically ill surgical patient are discussed frequently, especially when our colleagues in internal medicine are asked to see the patient in consultation. Internists are usually delighted if they can achieve normal cardiac outputs and normal oxygen consumptions in their critically ill patients. A CI of 3 $L/min/m^2$ in a patient with a recent myocardial infarction, for example, is more than enough. The heart in such a patient should be allowed to rest, and the total amount of tissue that might need extra perfusion for healing is relatively small (although, admittedly, the damaged tissue is located in a critical organ).

The septic or severely traumatized surgical patient, however, presents a different problem. The surgical patient may have kilograms of infected or injured tissue. This tissue needs augmented flow to curtail its infection or to heal its damaged cells. Furthermore, the surgical patient is likely to have at least some myocardial reserve. Surgical patients with *no* myocardial reserve do not survive their initial injury or operation.

Thus, the internist and surgeon bring different perspectives to the intensive care unit. One of the major contributions of the work of Shoemaker et al is that it provides evidence that the surgical patient does better with a supranormal CI, with its resultant supranormal delivery of oxygen to the tissues. Achieving these supranormal values may require the administration of large amounts of fluids, perhaps more than the internist feels comfortable with, but the Swan-Ganz catheter can settle any disagreements. The goal for most surgical patients, in contrast with medical patients, is a CI of 4.5 $L/min/m^2$ in a patient younger than age 50 years with good coronary arteries and a CI of 3.5 $L/min/m^2$ in an older patient with coronary disease. The wedge pressures can usually be kept around 12 mm Hg for patients who are being mechanically ventilated and around 7 mm Hg for those who are breathing without mechanical assistance. This study and previous studies from Dr Shoemaker's group represent the only attempts that I know of to deal with the critical question of what is the optimal CI in the surgical patient.

How were the supranormal CIs achieved? Supplementary tables indicate that the filling pressures were the same between the control and protocol patients, and the tables in the article indicate that fluid administration between the groups was also comparable. Were the protocol patients given no more fluid than the control group? How did the anesthesiologists use the Swan-Ganz information in treating the patients during surgery? The tables indicate that the intraoperative treatment of the groups was close to identical. Did the anesthesiologists use the CI as one of their principal end points or did they use the filling pressures? If they did use the CI, what values did they try to achieve, considering that the anesthetized patient probably does not require as much oxygen for tissue metabolism as the unanesthetized patient? The authors found that the patients who were maintained at high postoperative CIs were less likely to suffer later major organ failure. Have the authors attempted a more thorough statistical analysis than that described in this article? In particular, have the authors attempted to correlate postoperative organ failure with CI using, for example, multiple logistic regression? How long should a patient be kept in a hyperdynamic state? Our experience suggests that a few days is enough, assuming that the patient's postoperative recovery is uncomplicated. Last, were there any complications associated with insertion or use of the Swan-Ganz catheters? In particular, what was the incidence of catheter sepsis?

JOHN R. BENFIELD, MD, Sacramento: Study design and execution are interesting aspects of the work of Shoemaker et al because they are unspoken commentaries about the difficulties of doing clinical research in critically ill patients. Informed consent is hard to obtain, yet it is crucial that we have the information that such work will provide.

Among 146 patients eligible for random allocation to treatment to achieve normality compared with "supernormality," 88, or about 60%, were entered into the protocol. I see the cup as 60% full rather than 40% empty and congratulate Dr Shoemaker for his persistence in providing us with clinically relevant information. Pulmonary artery catheters for monitoring helped achieve the "supranormal" state and higher survival probability. The pulmonary circulation monitoring may have prevented harmful fluid overload.

Since there is a difference between young trauma victims and critically ill old patients insofar as their tolerance to overly aggressive resuscitation is concerned, it will be important in future studies to quantitate this difference. To what degree can one rely on the simpler methods of monitoring CVP, urine output, and body weight to achieve precise resuscitation tailored to the needs of an individual patient? How often, if at all, did pushing patients into the so-called supranormal state result in temporarily harmful side effects? Although CVP catheters are as effective and less costly than PA catheters in some patients, I believe prophylactic monitoring of physiologically impaired patients, particularly the elderly, with the use of PA catheters is worthwhile and fiscally responsible.

LOUIS L. SMITH, MD, Loma Linda, Calif: We frequently forget that the blood volume is contained in an elastic container that is also permeable. Certain toxemic states can produce a maldistribution situation resulting in the sequestration of large volumes of blood, particularly in the pulmonary circulation and postcapillary venules. When this occurs in the critically ill patient, additional blood volume is necessary if we are going to provide optimal cardiac filling pressures. Have the authors noted acute circulatory changes in patients in the control group following the induction of anesthesia? What volume of colloid was used in the different groups? It appeared that your treatment group received a greater amount of colloid than the control group.

KENNETH S. WAXMAN, Orange, Calif: Other research points to inflammatory mediators as the underlying cause of the hypermetabolic state. What is the role of inflammatory mediators and how does this concept fit with your data? Is there a difference between the hyperdynamic state of the early postoperative period and that following trauma, sepsis, and burns where most of the inflammatory mediator work has been done? If the hyperdynamic state is compensatory for ischemic tissue injury and is of survival value, and if it is physiologically important to have high cardiac output and high oxygen consumption, might therapeutic approaches designed to decrease these hemodynamic and metabolic responses be harmful?

C. JAMES CARRICO, Seattle, Wash: I am concerned about the randomization used. The proposal, as I understand it, is that the conversion of the patients' hemodynamic values to the supranormal state dramatically reduced the mortality from 43% to 4%. In the nonrandomized group, the CVP control group, and the PA control group a significant number of patients had septic shock. In contrast, in your PA protocol group, only one person was listed in the category of sepsis or septic shock. Could that explain the difference in outcome? Was there a quirk in the randomization that ended up with a very small number of people with sepsis in the PA protocol group and, thus, a much higher survival unrelated to treatment? I am not challenging the importance of monitoring and maximizing oxygen consumption. I am asking whether the dramatic difference in survival is related to a quirk in randomization rather than the therapy.

JONATHAN R. HIATT, MD, Los Angeles, Calif: Monitoring is of greatest value when instituted early. The patient who gets a Swan-Ganz catheter after surgery often represents a failure to recognize the need for monitoring. Patients who would benefit most from early monitoring are the critically injured trauma victims, particularly the elderly, yet monitoring is logistically difficult in a busy emergency department. What monitoring should we do in the emergency department at the outset of resuscitation and, in particular, when should invasive hemodynamic monitoring be begun?

DR SHOEMAKER: Drs Holcroft and Benfield have pointed out that we are looking at median values of the survivors to test our hypothesis. In fact, there is a range of survivor values, but we can only test a number, not a range. Therefore, this is an oversimplification. Moreover, the septic patient, the cirrhotic patient, and the patient who has preexisting trauma have high cardiac output values before surgery. The survivor patterns of those groups will have further increased compared with their own baseline values. Unfortunately, we have to oversimplify to test the hypothesis.

Dr Holcroft, on occasion we have raised the wedge pressure up to 18 to 20 mm Hg to achieve the goals of therapy. The volume of fluids used was very similar; greater amounts and higher percentages of colloids were used in the protocol patients to achieve the goals. A mean of 3 L of albumin was used, compared with less than half that amount in the control group. We do not want to advocate any particular therapy, but rather seek to observe the effects of two different therapeutic goals. For the purposes of this study, it does not matter how these goals are attained as long as they are reached promptly. In 68% of the cases in this study the goals were attained with fluids alone. In 32% of the cases we had to add an inotropic agent, usually dobutamine. In 7% of the cases we also used vasodilators.

The anesthesiologists and surgeons had agreed to the conditions of the study and had agreed to follow the protocol before, during, and after surgery. Before and during surgery we used the normal values because of the cardiac depression effects of most anesthetics, but in the immediate postoperative period the supranormal values empirically seen in survivors were used. The question about a more thorough analysis of postoperative patterns is very appropriate. Recently, we evaluated a series of 708 postoperative patterns more completely using some 30 different criteria for stratification. You are quite correct that the elderly patient, particularly the patient older than 70 years, does not need to achieve quite as high values. The question of how long is necessary to maintain optimal values is unanswered by these studies. However, we assume that 3 to 5 days is adequate. If the clinical condition is satisfactory, then we gradually lower the goals. If the patient develops sepsis, adult respiratory distress syndrome, or other complications, supranormal goals are maintained until recovery.

The complications from the Swan-Ganz catheter included transient premature ventricular complexes on insertion of the catheter in 12% of patients. Four septic patients had positive cultures, but they cleared up as soon as the catheters were removed. Five percent of patients had inflammation at the site of the insertion. There were no long-lasting or clinically harmful complications. Dr Smith, no patient in the series had a hypotensive episode while receiving anesthesia, but we have, of course, seen this. We think this really reflects an underlying preoperative hypovolemia. Usually this is demonstrated by low wedge pressures. Dr Benfield, we were unable to recognize tissue hypoxia, which we believe is the underlying problem in postoperative shock and organ failure, with the conventional blood pressure, urine output, body weight, and intake and output. For this reason, we had to resort to measurements of oxygen transport. Also, you correctly pointed out that we are looking at median values when they are really a range. When the median value is used, it implies that 49% of the survivors did not reach the median while 51% reached even higher values. In answer to questions about the complications, two patients in the PA-protocol group, one of whom had a high CVP with mitral disease before surgery, and three patients in the control group developed pulmonary edema. One patient in the protocol group and nine in the control group had adult respiratory distress syndrome. We do not think that the overadministration of fluid is much of a problem. Pulmonary edema is easily corrected, but adult respiratory distress syndrome still carries a 50% to 60% mortality. This, therefore, is the most important issue.

Dr Hiatt asked when to start the monitoring. We think that this is possible in the emergency department with noninvasive systems. It is hard to insert a Swan-Ganz catheter in the emergency department, but if there is time we recommend this be done before surgery. Dr Waxman, the inflammatory mediators are extremely important issues but they are different from the issues that we addressed. Usually the time differences separate the hyperdynamic states. We are addressing the immediate or very early increase in cardiac output in 2 to 12 hours. The inflammatory mechanisms often begin within 2 to 4 days or more after surgery and are associated with the septic hypermetabolic course from different mechanisms as well as specific mediators. Our concept is to prevent tissue hypoxia or, failing this, to rapidly correct the tissue hypoxia with aggressive therapy in the immediate period. Dr Waxman clearly pointed out that the hyperdynamic response may be an early compensation to tissue hypoxia, but the hyperdynamic state may subsequently reflect a septic pathologic state.

Dr Carrico, on the distribution of high-risk criteria between the control and protocol groups, the purpose and design of our study was to evaluate therapy in all high-risk patients, but because of the large number of criteria for high-risk patients and the limited number of study patients, there were inadequate numbers to evaluate this concept for each criterion. Moreover, there is a likelihood of bias in that there were three control patients but only one protocol patient with septicemia in the second series. However, in the first series, 31% of the protocol patients and 26% of control patients had septicemia.

Popliteal Vascular Trauma

A Community Experience

James J. Peck, MD; A. Brent Eastman, MD; John J. Bergan, MD; Marc M. Sedwitz, MD;
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• Preventing amputation continues to be a significant challenge when popliteal vascular injuries occur. A retrospective review of cases from the San Diego County (California) Trauma System identified 108 patients with 76 blunt and 32 penetrating arterial injuries. The limb preservation rate was 88%; there were 13 amputations. The fracture–dislocated knee injury and close-range shotgun blasts were particularly limb threatening. In general, the trauma system achieved rapid evaluation of injuries and early operative intervention. All 13 patients who underwent amputations presented with signs of severe ischemia. Concomitant injuries to the popliteal vein, tibial nerves, and soft tissue were significantly more frequent in patients who underwent amputations. The importance of complete fasciotomy for compartment hypertension, early reconstructive management of soft-tissue injuries, and expeditious arterial repair, frequently without preoperative roentgenographic suite arteriography, is emphasized. An aggressive, multidisciplinary approach is required to achieve a functional extremity when popliteal vascular trauma occurs.

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Injury to popliteal vasculature taxes the ingenuity and perserverance of the trauma surgeon. The importance of evaluating the popliteal artery in patients with penetrating injuries, dislocations, and fractures around the knee has become ingrained in vascular surgical practice. Although perigenicular vascular injury accounts for only 10% of vascular trauma, it causes 65% of the amputations.[1] Procrastination with such injuries threatens viability because of the failure to restore perfusion to the microcirculation within a period of ischemic tolerance. Salvage of these limbs with combined vascular, skeletal, and soft-tissue trauma requires a multidisciplinary approach. Management must be directed not only to the initial limb survival, but also to the eventual functioning of the extremity.

Morbidity and amputation in cases of popliteal vascular injury are related to a delay in recognition and treatment of these injuries. A well-organized civilian trauma system should facilitate the rapid identification and treatment of such patients and improve limb salvage if proper management techniques are observed. The purpose of this study was to review these goals in this regionalized trauma system.

PATIENTS AND METHODS

From January 1, 1985, until July 1, 1989, 108 consecutive patients with popliteal vascular trauma were admitted to one of five adult trauma centers in San Diego County, California. Four of these are level 2 community hospital trauma centers and one is a level 1 university hospital. Each hospital provided a 24-hour trauma team that included an in-house trauma surgeon. Triage protocols direct severely injured patients to these trauma centers.

All patients underwent a concurrent medical audit process using a computerized trauma registry. Charts were reviewed retrospectively by one of the authors (J.J.P.). All deaths and major complications were reviewed monthly by the Medical Audit Committee of the San Diego County Trauma System.[2] Two-tailed Fisher's Exact Test was used to compare patients who underwent amputations with those who did not. Differences were interpreted as statistically significant at $P<.05$.

RESULTS

Response Time

The mean prehospital time was 37 minutes, with a range of 9 to 82 minutes. Eighty-five percent of the patients were in the trauma center within less than 50 minutes after paramedics received the dispatcher's call.

Mechanism of Injury

There were 102 males and six females ranging in age from 16 to 59 years (mean age, 28 years). The mechanism of injury was blunt trauma in 76 patients (70%) and penetrating injuries in 32 patients (30%), as shown below:

Trauma	**No. of Patients**
Blunt	
Pedestrian	36
Motorcycle	16
Automobile	16
Falls	6
Industrial	2
Total	**76**
Penetrating	
Bullet wound	17
Knife/glass wound	10
Shotgun wound	5
Total	**32**

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Table 1.—Orthopedic Injuries in Popliteal Vascular Trauma

	No. of Injuries		
	Blunt (n=76)	Penetrating (n=32)	Total (N=108)
Knee fracture-dislocations	27	0	**27**
Knee dislocation alone	15	0	**15**
Tibia/femur fracture	34	10	**44**

Table 2.—Physical Examination Findings in Popliteal Vascular Trauma

	No. (%) of Patients		
Finding	Blunt (n=76)	Penetrating (n=32)	Total (N=108)
Palpable pedal pulses	5 (7)	6 (19)	**11** (10)
No palpable pedal pulses	71 (93)	26 (81)	**97** (90)
Severe ischemia	48 (63)	22 (69)	**70** (65)

Table 3.—Preoperative Angiography in Popliteal Vascular Trauma

	No. (%) of Patients		
Location	Blunt (n=76)	Penetrating (n=32)	Total (N=108)
Radiology department	38 (50)	25 (78)	**63** (58)
Operating room	28 (37)	6 (19)	**34** (32)
None	10 (13)	1 (3)	**11** (10)

Associated Injuries

Multisystem injuries occurred in 42 patients with blunt trauma and five patients with penetrating injuries. These included closed-head injuries, intra-abdominal trauma requiring exploratory celiotomy, and cardiac or pulmonary contusions. The associated orthopedic injuries are recorded in Table 1.

Physical Findings

Findings on the initial physical examination are shown in Table 2. Eleven patients (10%) had a significant vascular injury and yet maintained palpable distal pulses. Severe ischemia was manifested by a cool, pulseless foot, with sensory and motor deficit (Table 2). Angiography was performed prior to surgery in 97 patients (90%) (Table 3).

Operative Findings and Repair

Vascular repair was accomplished in 107 of the 108 patients. One patient underwent immediate amputation of a severely crushed extremity with avulsion of the popliteal artery and vein and the posterior tibial nerve.

The time from admission to surgery averaged 2 hours 45 minutes for patients with blunt trauma and 2 hours 55 minutes for patients with penetrating injuries. Intimal injury with thrombosis or transsection of the popliteal artery occurred in 96% of patients with blunt trauma and 81% of patients with penetrating injuries (Table 4). Pseudoaneurysm formation or arteriovenous fistulas were seen in six patients with penetrating trauma and three patients with blunt injuries.

Table 4.—Operative Findings in Popliteal Vascular Trauma

	No. (%) of Patients		
Finding	Blunt (n=76)	Penetrating (n=32)	Total (N=108)
Artery thrombosed	38 (50)	10 (31)	**48** (44)
Artery transsected	35 (46)	16 (50)	**51** (47)
Pseudoaneurysm	2 (3)	3 (9)	**5** (5)
Arteriovenous fistula	1 (1)	3 (9)	**4** (4)
Trifurcation arteries also involved	24 (32)	4 (13)	**28** (26)
Popliteal vein also involved	18 (24)	9 (28)	**27** (25)

Table 5.—Vascular Repair in Popliteal Vascular Trauma*

	Arterial Repair		
	Blunt (n=75)†	Penetrating (n=32)	Total (N=107)†
Primary end-to-end	30 (40)	20 (63)	**50** (47)
Vein interposition graft	33 (44)	8 (25)	**41** (38)
Vein bypass graft	10 (13)	3 (9)	**13** (12)
Vein patch	2 (3)	1 (3)	**3** (3)
	Venous Repair		
	(n=18)	(n=9)	(N=27)
Primary end-to-end	6 (33)	1 (11)	**7** (26)
Vein interposition graft	2 (11)	1 (11)	**3** (11)
Lateral venorrhaphy	2 (11)	2 (22)	**4** (15)
Ligation	8 (44)	5 (55)	**13** (48)

*Numbers are the No. (%) of patients.
†One primary amputation.

The types of repair are listed in Table 5, with primary end-to-end repair occurring in 63% of penetrating injuries compared with 39% of blunt injuries. The popliteal vein was repaired in 10 of 18 patients with blunt trauma and four of nine patients with penetrating injuries. Fogarty catheters were passed in all but one patient. One hundred and three revascularized patients (96%) were given heparin during surgery. In 19 patients (18%) regional heparin alone was administered, and in 84 patients (82%) systemic heparin was administered.

Operative Adjuncts

Four-compartment fasciotomies were performed in 54% of blunt injuries and 28% of penetrating injuries, with long dermotomies in all but seven patients. In 77% of the patients external fixators were used for skeletal stabilization for fractures and dislocations. Vascular repair preceded orthopedic stabilization in 88% of patients with blunt trauma and 100% of patients with penetrating injuries with fractures. An intraluminal shunt was used in five of the nine patients who required orthopedic stabilization before vascular repair because of a flail extremity. Eighteen patients had complex soft-tissue defects that subsequently required muscle flaps for coverage. Soft-tissue infections occurred in 36 patients (42%) with blunt trauma and six patients (19%) with penetrating injuries.

Morbidity and Mortality

In the 107 patients who underwent arterial reconstruction, 97 had durable anastomotic repairs. The limbs of five patients could not be salvaged by reoperation and five other patients did not undergo reexploration. All 10 of these patients underwent amputation. Technical errors occurred in three other cases and these injuries were successfully repaired by reoperation. There was an intimal flap in two patients and an inadequate fasciotomy in one patient.

The limb preservation rate was 88%. All 13 patients who required amputation were in the subset of 70 severely ischemic patients who presented with a cool, pulseless foot and neurologic deficit. Eleven amputations occurred in patients with blunt trauma. Seven had fracture dislocations of the knee, three had tibial plateau fractures, and one had a knee dislocation without fracture. Two amputations occurred in patients with penetrating injuries; both sustained close-range shotgun wounds.

Concomitant injuries to the vein, nerve, or soft tissue were significantly more frequent in the 13 patients with amputated limbs. The vein was transsected or thrombosed in nine patients ($P>.05$). Nerve injury in the popliteal fossa was identified in nine patients ($P>.05$). Extensive soft-tissue injury with crushed muscle, avulsion, or stripping of the periosteum was present in 12 patients ($P>.05$).

Eleven of the 13 patients who underwent amputation had an interposition or bypass venous graft. The overall amputation rate with this form of arterial reconstruction was 11 (20%) of 54 patients. Primary end-to-end repair failed in one (2%) of 50 patients.

The mean time between admission and surgery, age, injury severity score, and involvement of distal tibial vessels were no different for patients with amputated limbs than for the entire series ($P>.05$). There were no amputations in the 38 good-risk patients presenting with a viable foot and, as a group, they had longer intervals from admission to surgery than severely ischemic patients. The numbers were too small to show statistical significance for age, injury severity score, and tibial vessel involvement.

The 13 patients who underwent amputation were scrutinized for technical and judgmental errors that may have led to limb loss, as shown below:

Reason for Amputation	No. of Patients
Unsalvageable limbs	4
Error in diagnosis	2
Error in judgment	2
Error in technique	2

Four patients were judged to have unsalvageable limbs. One underwent a primary amputation because of an avulsed posterior tibial nerve. Three others underwent delayed amputations within 48 hours after the initial exploration and vascular anastomosis because of unsalvageable soft-tissue–crush injuries with small-vessel thrombosis. Nine (69%) of 13 patients had potentially preventable amputations.

Errors in diagnosis occurred in two cases in which there was delayed recognition of anastomotic thrombosis and no reoperative effort. Errors in judgment occurred in two cases. Both patients underwent radiographic suite arteriography despite presenting signs of severe ischemia. This delayed revascularization for 2 and 3 hours, respectively. Finally, errors in technique occurred in five cases. In two of these patients, fasciotomies and dermotomies were not performed during the original procedure. One patient had a primary end-to-end repair under tension that could not be salvaged with a later interposition graft. Two patients had patent arterial repairs but developed sepsis from soft-tissue myonecrosis. More aggressive early débridement of devitalized tissue might have saved the limbs. There were two deaths. One was due to a severe head injury and the other was secondary to pulmonary embolism. Both deaths were determined to be nonpreventable.

Functional Recovery

Ninety-three patients were alive with limb salvage. In-hospital ambulation was achieved prior to discharge in 79 (85%) of these patients. Sixty-six patients walked without assistance and 13 required a cane or walker. Fourteen patients (15%) were unable to walk. Six had closed-head injuries and eight were transferred to rehabilitation facilities for complex orthopedic and soft-tissue injuries. All patients with stab wounds or low-velocity gunshot wounds became ambulatory.

COMMENT

During World War II, primarily penetrating popliteal arterial injuries were treated by ligation. This led to a 73% amputation rate.[3] Experience with arterial repair and reconstruction in the Korean conflict lowered this rate to 32%.[4] In the Vietnam conflict, this rate remained at 29%.[5] Management in civilian practice has been more discouraging, with a reported amputation rate of 42%.[6] Recently, the civilian experience has been encouraging, with a decline in amputation rates from 15% to 0%.[7-9]

Civilian trauma managed in the San Diego County Trauma System resulted in an 88% limb preservation rate in patients with popliteal arterial injuries. In general, an efficient prehospital system resulted in rapid evaluation and early operative intervention. The unstable knee injury and close-range shotgun blasts were found to be particularly limb threatening. All amputations occurred in extremities presenting with a cool, pulseless foot and neurologic deficit. In such cases of severe ischemia that were noted preoperatively, radiographic suite arteriography was found to be unnecessarily time-consuming. We reemphasize the importance of complete fasciotomy for compartment hypertension and aggressive treatment of soft-tissue injuries. Arterial wounds from low-velocity missile injuries or stab wounds were expeditiously repaired and had a 100% limb salvage rate. Amputations were associated with complex orthopedic and soft-tissue injuries.

Early identification of vascular injury in blunt trauma required a high index of suspicion and careful evaluation for signs of distal ischemia. In the review by Snyder,[10] arterial injuries occurred in 30% to 50% of knee dislocations, 2% of tibia fractures, and 0.5% of femur fractures. The popliteal artery is tethered between the distal femoral shaft and the proximal tibia by the tendinous arch of the adductor magnus proximally and the soleus muscle distally (Fig 1). This anatomy makes it susceptible to stretch injury while not protecting the vessels from direct trauma. The perigenicular collaterals around the knee are easily avulsed or thrombosed by high-energy impact or blunt trauma.

This study identifies the treacherous potential of fracture dislocations of the knee, which had a 26% amputation rate. Extreme force, from 650 to 800 psi, is required to dislocate or fracture the knee.[11] Posterior dislocations were more frequent because of the high incidence of bumper and dashboard injuries. They frequently cause a clean, short, intimal fracture from the sharp edge of the posterior tibial plateau (Fig 2). Anterior dislocations are due to hyperextension injuries and result in the stretching of a long segment of artery.

The decision to perform a primary amputation is difficult and was made in only one of the patients in this study. The indications for primary amputation included the following: (1) a posterior tibial nerve transsection with an anesthetic, paralyzed leg; (2) a crush injury with prolonged warm ischemia; and (3) other life-threatening injuries that made immediate amputation prudent. Rarely is the vascular injury the deciding factor. Recently, several authors[12,13] have attempted to predict occurrences of the irretrievable extremity. The accuracy of these objective criteria needs further evaluation. Both

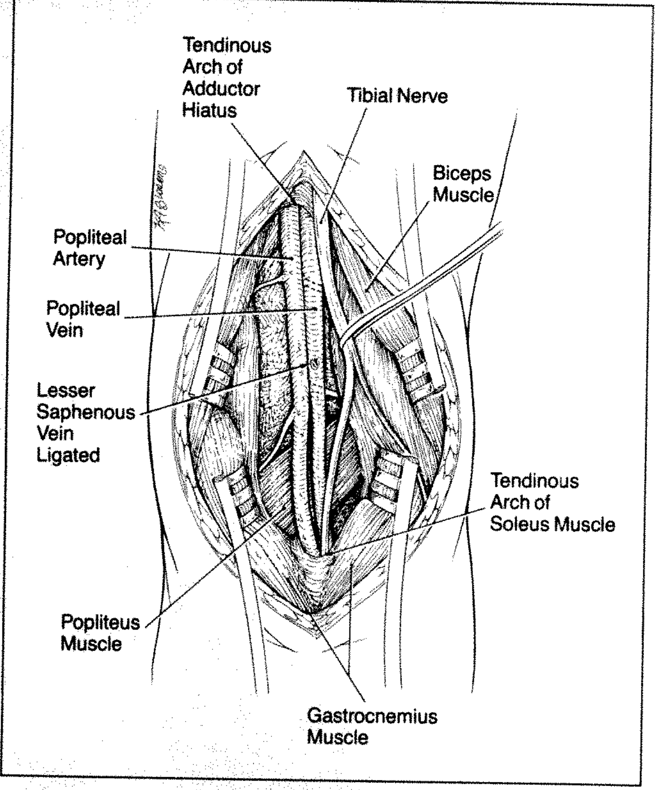

Fig 1.—The popliteal artery is tethered between the tendinous arches of the adductor magnus proximally and the soleus muscle distally. The popliteal vein is posterior and lateral to the artery (right leg).

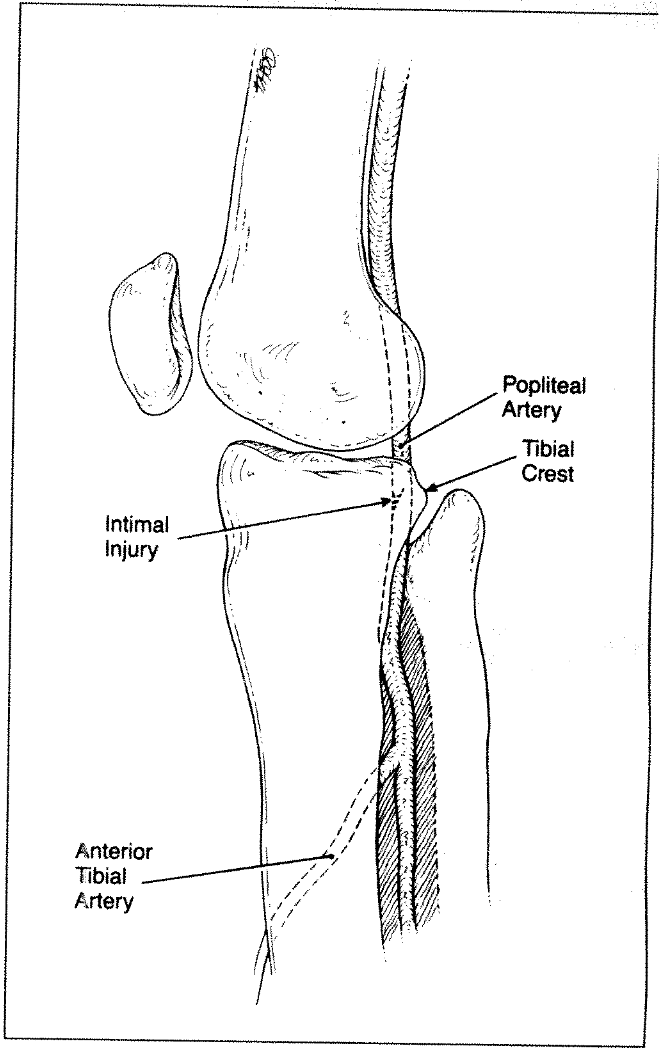

Fig 2.—The anatomic relationship of the tibial plateau and the popliteal artery. Bumper and dashboard injuries with posterior dislocations or tibial plateau fractures can result in intimal injury with thrombosis or transection of the popliteal artery.

the mangled extremity severity score and the mangled extremity syndrome index misidentified eight patients each in this series.

Most injuries were approached medially, but a posterior approach gave excellent exposure in 20 patients with midpopliteal artery injuries. The choice of approach was an individual one made in each case by the operating surgeon. A venous interposition graft from the contralateral extremity is generally the best method of reconstruction. A primary end-to-end arterial repair was done in 50 of these patients, with only one amputation. In contrast, the amputation rate was 20% for cases in which venous grafts were used to repair the artery. The reason for this was the extent of the arterial injury and associated trauma. The end-to-end repairs had shorter arterial injuries and less soft-tissue trauma. Five end-to-end repairs had to be revised with a vein graft. This caused one amputation that may have been avoided.

Concomitant or prior popliteal venous repair has been thought to enhance the success of the arterial reconstruction by facilitating runoff and decreasing compartment pressures.[14] It is thought that even temporary patency is beneficial in avoiding acute venous hypertension, distal compartment syndromes, and edema. Late postphlebitic sequelae may be prevented. Fourteen patients had popliteal venous repairs and 13 had ligation. No clear benefit from venous repair was noted in this small number of patients, with four amputations in each group.

Preoperative arteriography should be used selectively for patients without severe distal ischemia. Emergency department and operating room angiography is less time-consuming.[15] Routine, postreconstructive, intraoperative arteriography is wise. A completion arteriogram will determine the technical adequacy of the anastomosis, more distal injuries, and patency of distal runoff vessels. Postoperative surveillance for anastomotic thrombosis must be meticulously monitored in an intensive care unit.

Patients with a delay in vascular reconstruction of greater than 4 hours or with combined arterial and venous injuries usually require fasciotomy, frequently prior to the arterial repair. The importance of fasciotomy was highlighted by two patients whose fasciotomies were not done during the initial operation and who subsequently underwent amputation. In this study, 70% of knee dislocations required fasciotomies. Double-incision, four-compartment fasciotomies with dermotomies are most efficacious.[16]

The extent of soft-tissue trauma was an important determinant of limb salvage. Thorough débridement of the devitalized tissue is critical, and a second-look procedure 24 to 48 hours later has been recommended.[10] In the most successfully managed cases of soft-tissue injuries, a plastic reconstructive surgeon was involved in the initial operation. Early coverage of high-energy wounds optimizes wound healing by decreasing wound infection and the chance of chronic osteomyelitis.

External fixations for orthopedic stabilization were used in 77% of cases. The fractures were often complex and had been contaminated. External fixation facilitates postoperative access to the wounds for treatment of soft-tissue injuries and monitoring of the distal circulation. Internal fixation can be time-consuming and may jeopardize collaterals because of the need for further dissection.

Arterial injuries should be repaired prior to the orthopedic stabilization. Placement of orthopedic hardware prolongs ischemia time, frequently interferes with the vascular repair, and can obscure visualization of the blood vessels on postreconstructive arteriography. However, very unstable fractures may require fixation prior to vascular repair. An intraluminal shunt has been recommended by Johansen et al[17] to restore perfusion in a small subset of patients. In this present study, it was used successfully in five patients.

Several lessons were learned from the patients with a potentially preventable amputation: (1) When severe ischemia is seen on admission, arteriography, if mandatory, should not delay revascularization. (2) Postoperative surveillance for anastomotic thrombosis must be conscientiously monitored with prompt reoperation. (3) Fasciotomies are frequently required, especially in patients with combined venous and arterial injuries or delayed arterial repair. (4) End-to-end arterial reconstructions are for short injuries and should be avoided if there is tension on the repair. (5) Aggressive débridement of devitalized soft tissue and early plastic surgical intervention is recommended to address the problems of myonecrosis and subsequent sepsis.

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Discussion

ALBERT E. YELLIN, MD, Los Angeles, Calif: One hundred years ago, John Hunter wrote, "Amputation is a violence, superadded to the injury." In this series of 108 patients with popliteal trauma treated in five community trauma centers in San Diego, Calif, with a limb salvage rate of 88%, there were 13 amputations, nine of which, according to the authors, were possibly preventable. Twelve of these 13 patients had severe soft-tissue injuries and many presumably developed limb sepsis.

In more than 200 patients with popliteal trauma treated at the Los Angeles County/University of Southern California Medical Center during the past 20 years, there has been a marked increase in limb salvage in the last decade. Variables such as time to the operating room, knee dislocation, fracture, trifurcation injury, preoperative compartment syndrome, fasciotomy, and vein injury did not correlate with outcome.

Severe soft-tissue injury was present in 31 patients, 13 of whom underwent amputation, whereas only two of 69 patients without soft-tissue injuries underwent amputation. Deep infection occurred in 17 patients, nine of whom underwent amputation. These were ominous predictors. In addition, preoperative ischemia predicted poorer results; primary repairs did better than vein grafts, but this was more a reflection of the lesser magnitude of the injury than the method of repair. The use of systemic heparinization clearly was associated with greater limb salvage.

Our amputation rate dropped from 23% to 6% after 1980 ($P<.05$). Two variables stand out as being significant. They are the more frequent use of intraoperative heparinization and the reduction in subsequent development of deep infection. Whether we are treating patients with penetrating or blunt trauma, complex soft-tissue wounds and subsequent infection resulted in the majority of limb loss, despite a successful vascular repair with palpable distal pulses present at the time of amputation.

If we are to achieve better results, they will relate mostly to our ability to prevent and treat soft-tissue infection. This means initial aggressive débridement of all devitalized tissue, coverage of exposed vessels, immediate grafting of fasciotomy sites, and a prompt return to the operating room for further débridement at the first sign of postoperative sepsis. Reconstructive surgeons should be involved early to help make decisions regarding coverage of complex injuries.

This presentation analyzes and reports the collaborative efforts of many surgeons in multiple trauma centers in an excellent trauma system designed to get the right patient to the right hospital in the right time, where, we hope, the right operation will be performed. However, if the right operation is not performed, the problem will be identified through a comprehensive quality assurance review process designed to correct the problems identified and prevent repetition. This is perhaps the most important lesson to be learned. How many limbs that were later lost became infected? Do you attempt to cover all open wounds and fasciotomy sites? Do you reoperate early for repeated débridement? What will you do differently in the future or how will you use the information gleaned from this review?

ROGER E. ALBERTY, MD, Portland, Ore: Many articles report dismal amputation rates in cases of popliteal artery injuries, and it is rather hard to regulate the surgical community. In the authors' trauma system, they anticipate that they will be able to establish protocols. Most vascular surgeons know how to fix arterial injuries. It is the whole package that needs to be addressed.

STEPHEN N. ETHEREDGE, Oakland, Calif: A group of us in the Bay area had six cases of iatrogenic popliteal injury during a 2-year span. These injuries are caused by orthopedists in the course of doing either open meniscectomies or, now more commonly, closed arthroscopic surgery. The danger of this injury is that it is frequently unrecognized. When the orthopedist says, "I think I have injured the popliteal artery," I strongly recommend that he or she administer heparin prior to letting down the tourniquet. If heparin is not administered, the blood that fills the dry tissues will be very hypercoagulable.

Frequently, injuries of this sort are not recognized until the following morning. In these cases, we have found it helpful to add intraoperative urokinase infusion to the primary procedures of Fogarty catheter thrombectomy and bypass revascularization. The object of delayed revascularization is to restore blood flow to the nutrient capillary bed as well as to the major vessels. Have the authors used urokinase in any of their patients and would it not have helped them save the limbs of 10 patients who had operative misadventures?

JAMES G. HOLMES, MD, Lafayette, Calif: In 1959, while at the Karolinska Institute, Sweden, I learned from Professor Erhup of the original three cases of a disease that he called cystic degeneration of the popliteal artery, a new entity. The disease involved a degenerative process in the media of the popliteal artery, with the formation of a cyst that impinges on the lumen of the vessel, causing ischemia in the distal extremity and even occlusion, with all the complications thereof.

In 1962, I described the first case in the American literature of a 25-year-old truck driver with acute ischemia of the leg. Arteriography showed a very smooth compression of the lumen of the popliteal artery, and during surgery the obstructing lesion proved to be a cyst in the media of the popliteal artery, which was successfully removed with no interruption of the intimal layer. More than 20 years later, this patient has no difficulty or arterial problems with that extremity.

This is another type of popliteal artery injury. A national registry for this disease was inaugurated by Drs Bergan and Yao at the Northwestern University School of Medicine, Chicago, Ill, and it has accumulated a significant number of cases. The common factor is that this entity should be suspected in patients whose profession involves repeated or prolonged acute bending of the knee.

ROBERT J. STALLONE, MD, Oakland: About 15 years ago, I saw a 48-year-old man who was in a vehicular accident. He had a fractured right scapula and no other chest or abdominal injuries. He also had a large ecchymotic area around his right knee and a cold, pulseless, right leg. An arteriogram confirmed a thrombosis of the proximal popliteal artery, with no flow distally. At exploration we found ecchymosis coming down from the thigh, but the popliteal fossa looked entirely normal and the pulse was absent distally. An embolectomy restored flow to the foot and removed an organized thrombus. The next morning an arteriogram demonstrated a transection of the thoracic aorta. The patient had an embolism from an intimal flap. In cases of blunt trauma, especially in elderly people, aneurysms or sclerotic vessels can rupture and embolize.

LUCIAN BUSCAGLIA, Stockton, Calif: What adjuncts to venous repair were most useful, and in the absence of other life-threatening injuries, how far would you take your efforts at venous repair? In children, would you consider the use of primary repair by extensively mobilizing the popliteal artery?

WILEY F. BARKER, MD, Los Angeles: It is most distressing to have accomplished a perfect technical reconstruction only to find that there is inadequate distal perfusion, the situation known as the syndrome of reperfusion injury. Dr Quinones-Baldrich's work has shown the value of thrombolysins to ensure complete small-vessel patency and perfusion.

Twenty-five years ago I used some of the primitive thrombolytic products in a few acute arterial obstructions after relieving the major problem, with moderately good results. I realize that this may not be applicable in the presence of some of the terrible penetrating soft-tissue injuries that have been shown, but in many blunt injuries or other acute circumstances the failure to accomplish perfect reperfusion may be as much the problem initially as the reperfusion problem a little later.

DR PECK: The purpose of this study was to develop a protocol for the San Diego County Trauma System. Each month the trauma directors of the six member hospitals review all deaths and complications. At the Medical Audit Committee meeting, deaths are judged to be nonpreventable, potentially salvageable, or, frankly, preventable. Complications are classified as due to delays in diagnosis; patient disease; or errors in diagnosis, judgment, or technique. This study takes the quality assurance process one step further.

Dr Yellin, we recommend early and systemic heparinization to prevent distal thrombosis if the other injuries do not preclude its use. Ninety-six percent of our patients underwent anticoagulation, most systemically. Nineteen patients received regional heparin. Preoperative arteriography can be unnecessarily time-consuming. The importance of soft-tissue management with a multidisciplinary approach was highlighted by this study. The plastic surgeon should often be involved at the initial operation, with second and subsequent débridement required at 24- to 48-hour intervals thereafter. Early soft-tissue coverage, often at the initial operation, will reduce soft-tissue septic complications. Two patients had patent arterial repairs, but underwent potentially preventable amputations, the result of myonecrosis and sepsis. We prefer four-compartment fasciotomy done through two longitudinal dermotomies, anterolateral and posteromedial, to the tibia, with early or immediate split-thickness skin-graft coverage.

Dr Buscaglia, venous repairs must frequently be more precise than arterial repairs because of the slower flow and lack of vessel-wall compliance. Contralateral saphenous-vein interposition grafts are often required. Lateral repairs with any resultant stenosis are doomed to result in thrombosis. After surgery, many authors recommend low-molecular-weight dextran, used in five of our patients, and/or heparin to maintain the patency of the venous repair. In this series, no spiral or prosthetic grafts were used. It is our impression that venous repairs are less important in patients who undergo prompt reconstruction. The Viet Nam experience reported by Rich et al[5] was associated with prolonged ischemic times. This report did not include any children, but we agree that end-to-end repair would be preferred. Autogenous tissue is essential to prevent stenosis as the child grows.

Dr Etheredge, we agree that the prompt use of heparin is important with iatrogenic popliteal arterial injuries that occur at the time of arthroscopy. Caution is needed with thrombolysins administered in the patient with multiple trauma. Dr Stallone, we have seen bullet embolisms to the popliteal artery from thoracic gunshot wounds. Dr Holmes, popliteal occlusion in young adults does have a fascinating differential diagnosis. Dr Barker, we have aggressively treated reperfusion syndrome with mannitol, bicarbonate, and elevation. Venous repair should improve outflow. Six of our patients received regional mannitol, as recommended by Shah et al.[9] Expeditious arterial repair is the best prophylaxis.

Utility of Computed Tomography for Surveillance of Small Abdominal Aortic Aneurysms

Preliminary Report

William C. Krupski, MD; Arie Bass, MD; Dennis W. Thurston, MD; Ralph B. Dilley, MD; Eugene F. Bernstein, MD, PhD

• To assess the ability of computed tomography to predict the potential for expansion of small abdominal aortic aneurysms, we analyzed the computed tomographic scans of 30 patients who had two or more abdominal computed tomographic scans at least 6 months apart between 1979 and 1989. Clinical variables and 10 defined objective characteristics of computed tomography were evaluated. Twenty-five men and five women with abdominal aortic aneurysms ranging from 30 to 64 mm (mean, 45 mm) were followed up with serial computed tomographic scans for a mean (± SE) of 26 ± 3 months. In 19 patients, enlargement of aneurysm diameter of 3 mm or more on serial computed tomographic scans was noted, whereas in 11, there was little or no expansion. Of the clinical variables studied, only serum cholesterol correlated with an increased risk of expansion. Thrombus area, measured by computed tomography, was 7.3 ± 0.9 cm^2 in enlarging aneurysms vs 4.3 ± 0.9 cm^2 in stable aneurysms. Based on these preliminary data, we conclude that computed tomography may provide valuable information about the likelihood of future expansion of small abdominal aortic aneurysms.

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Abdominal aortic aneurysms are vascular lesions frequently encountered in clinical practice. Selectivity in recommending operative repair of aortic aneurysms has been based on studies correlating the risk of rupture with aneurysm diameter.[1-5] Although the generally accepted average rate of enlargement for abdominal aortic aneurysms is 0.5 cm/y,[6,7] published mean expansion rates and individual aneurysm expansion rates vary widely. Littooy et al[8] reported a mean expansion rate of 0.79 cm/y in 149 abdominal aortic aneurysms followed by sequential B-mode ultrasonography, whereas Nevitt et al[9] described a rate of only 0.21 cm/y in 103 abdominal aortic aneurysms. Several investigators have examined the influence of various clinical variables on enlargement rates of abdominal aortic aneurysms. Diastolic blood pressure, initial aneurysm anteroposterior diameter, and obstructive pulmonary disease were independently predictive of aneurysm rupture in 67 patients with small aneurysms followed up for an average of 3 years.[10] In addition, the presence of coexistent distal occlusive atherosclerosis and an increased ratio of the aneurysm diameter to the aortic diameter have been correlated with increasing mean expansion rates.[11]

Most previous studies of abdominal aortic aneurysm expansion rates have been based on B-mode ultrasound measurements of size. While this method accurately measures abdominal aortic aneurysms,[8,12] computed tomography (CT) not only provides precise size, position, configuration, and anatomic relationship information, but also characterizes aortic wall composition and internal architecture. Computed tomographic scans have been useful for diagnosing abdominal aortic aneurysms,[13,14] planning therapy,[7,15-17] and following up patients postoperatively.[18]

Based on this capability to anatomically define the internal structure of abdominal aortic aneurysms in a detailed fashion, the present study was designed to examine the influence of several CT characteristics on abdominal aortic aneurysm expansion rates and subsequent outcome in a group of patients with small abdominal aortic aneurysms initially selected for nonoperative management. By this analysis we hoped to determine which CT scan characteristics would predict these rates and thus influence clinical management.

PATIENTS AND METHODS

The abdominal CT scans of 30 patients with abdominal aortic aneurysms who had two or more scans at least 6 months apart between January 1, 1979, and June 1, 1989, were analyzed. An abdominal aortic aneurysm was defined as enlargement of the infra-

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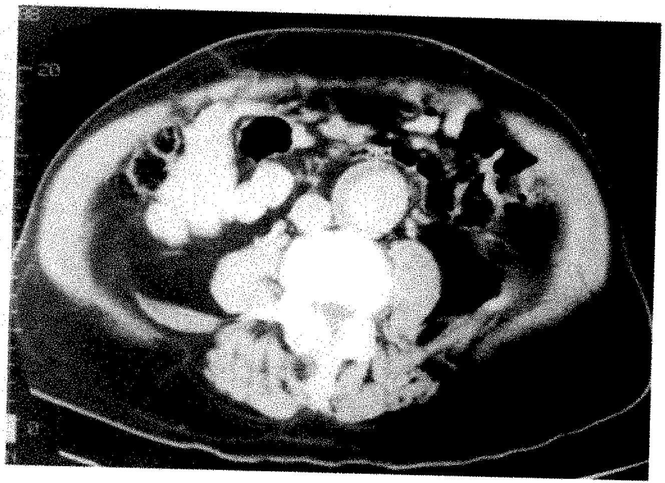

Fig 1.—Computed tomographic scan depicts an abdominal aortic aneurysm with minimal luminal thrombus. Computed tomography variables are as follows: aneurysm diameter, 34 mm; lumen area, 572 mm^2; thrombus-lumen ratio, 0.59; lumen diameter, 27 mm; thrombus area, 335 mm^2; thrombus arc, 0° to 360°; aneurysm area, 907 mm^2; lumen, central; calcification, 2+ (mosaic).

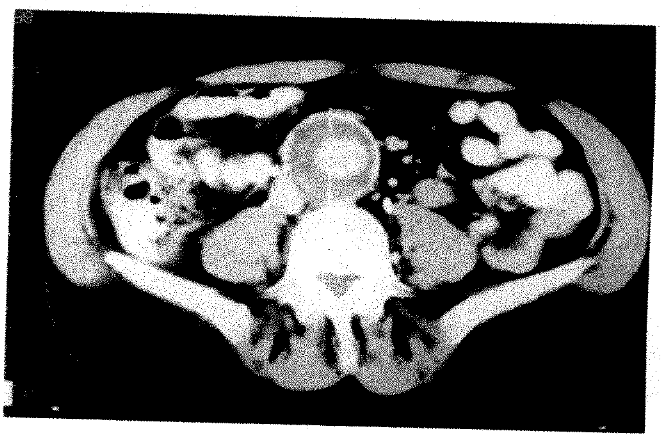

Fig 2.—Computed tomographic scan shows an abdominal aortic aneurysm with a large thrombus area. Variables are as follows: aneurysm diameter, 50 mm; lumen area, 615 mm^2; thrombus-lumen ratio, 2.1; thrombus to aneurysm ratio, 0.68; lumen diameter, 28 mm; thrombus A, 1347 mm^2; thrombus arc, 0° to 360°; aneurysm A, 1962 mm^2; lumen, left; calcification, 4+ (continuous).

renal aortic diameter to more than 1.5 times the proximal abdominal aortic diameter. Patients with suprarenal aneurysms, those who did not have contrast-enhanced CT scans, or those who underwent operative repair prior to serial scanning were excluded from the study. The initial decision to manage patients nonoperatively was based on absence of symptoms, small aneurysm size, or high operative risk. Subsequent decisions to pursue operative therapy were made individually.

Clinical data were extracted from patient records. Variables analyzed included gender, age, symptoms, presence and severity of hypertension, heart disease, peripheral vascular occlusive disease, diabetes mellitus, chronic pulmonary disease, smoking history, medications (with specific reference to β-blockade), and serum lipid levels.

CT Scans

Computed tomographic scans were performed using a whole body scanner (CT 9800, General Electric, Milwaukee, Wis) with scanning times of 2 seconds and slice thickness of 1 cm. Since the CT scans were not obtained prospectively, there was some variation in the contrast enhancement techniques employed. Images were obtained from the pelvis to the diaphragm. All scans were evaluated without knowledge of clinical features or patient outcome.

Measurements of aneurysm size and architectural information about the aneurysm were obtained at the level of greatest aneurysm diameter. Ten CT scan variables were analyzed, defined as follows:

1. Maximum diameter of the aneurysm was obtained by measuring the longest straight line drawn between opposing points on the aneurysm wall.
2. Lumen diameter was obtained by measuring the longest straight line between opposing points of the contrast within the aneurysm.
3. Aneurysm area was calculated by assuming that the aneurysm was a geometric circle and multiplying the square of the aneurysm diameter divided by 2 by π (Area $= \pi r^2$).
4. Lumen area was calculated as above, using lumen diameter divided by 2.
5. Thrombus area was derived by subtracting lumen area from aneurysm area (Figs 1 and 2).
6. The ratio of thrombus to lumen (T:L) was computed from respective area determinations.
7. The ratio of thrombus to aneurysm (T:A) was computed from respective area determinations.
8. Lumen location was identified as the predominant position of the contrast within the aneurysm (ventral, dorsal, lateral [left or right], or central).
9. Calcification was assigned a value from 1+ to 4+ according to its extent, as described by Pillari et al.[19] Minimal calcification was designated 1+ (Fig 3, top), whereas calcium surrounding the aneurysm was graded 4+ (Fig 3, bottom). Intermediate degrees of calcification were graded appropriately (eg, calcification around one half of the aneurysm, 2+). In addition, calcification was classified as continuous or intermittent (mosaic).
10. Arc of thrombus[19] was expressed in degrees (0° to 360°). This represented the configuration of the blood clot and debris adherent to the aortic wall. For example, if the lumen was central in the aneurysm, arc of thrombus was 360°, and in an aneurysm with a large eccentric lumen, arc of thrombus became progressively smaller.

The overall aneurysm expansion for each patient was calculated as the difference between the first and last maximum aneurysm diameter on CT scan. The expansion rate was determined by dividing this figure by the elapsed time interval between the first and last CT scan.

Patient Population

Thirty patients (25 men and 5 women) from 34 to 95 years of age (mean ± SE, 74 ± 2 years) with abdominal aortic aneurysms ranging from 3.0 to 6.4 cm (mean, 4.5 ± 1.3 cm) were initially managed nonoperatively. Two (7%) patients had symptoms of low back pain that were unrelated to the aneurysm but led to its detection. All other abdominal aortic aneurysms were discovered on routine physical examinations (7 patients) or found incidentally while patients were being evaluated for unrelated problems (21 patients). Hypertension was being treated in 18 (60%) patients. In spite of antihypertensive treatment, systolic blood pressure greater than 140 mm Hg was present in 13 (43%) patients and diastolic blood pressure greater than 90 mm Hg was present in 10 (33%) at the initial time of abdominal aortic aneurysm diagnosis. Overall mean blood pressure was 148 ± 87/7 ± 3 mm Hg. Coronary artery disease occurred in 17 patients (57%); nine patients (30%) had previous myocardial infarctions, and eight patients (27%) had symptoms of anginal pectoris. Peripheral vascular occlusive disease was manifested by claudication in nine patients (30%) and by previous amputation in one patient (3%). Diabetes mellitus was present in five patients (17%), only one of whom required insulin. Chronic obstructive pulmonary disease occurred in 14 patients (47%). Fifteen patients (50%) were taking oral β-blocking medication to treat hypertension or coronary artery disease. A history of cigarette smoking was given by the vast majority of patients (27 [90%] patients), but 16 (53%) quit on or about the time of discovery of their aneurysm. Of current or previous smokers, the mean smoking history was 51 ± 6 pack-years. Serum cholesterol levels averaged 6.80 ± 0.64 mmol/L and serum triglycerides averaged 2.82 ± 1 mmol/L.

Statistical Analysis

Data were coded and computerized for statistical analysis using the CLINFO Plus computer program provided by the Division of Research Resources, Heart, Lung, and Blood Institute, National Insti-

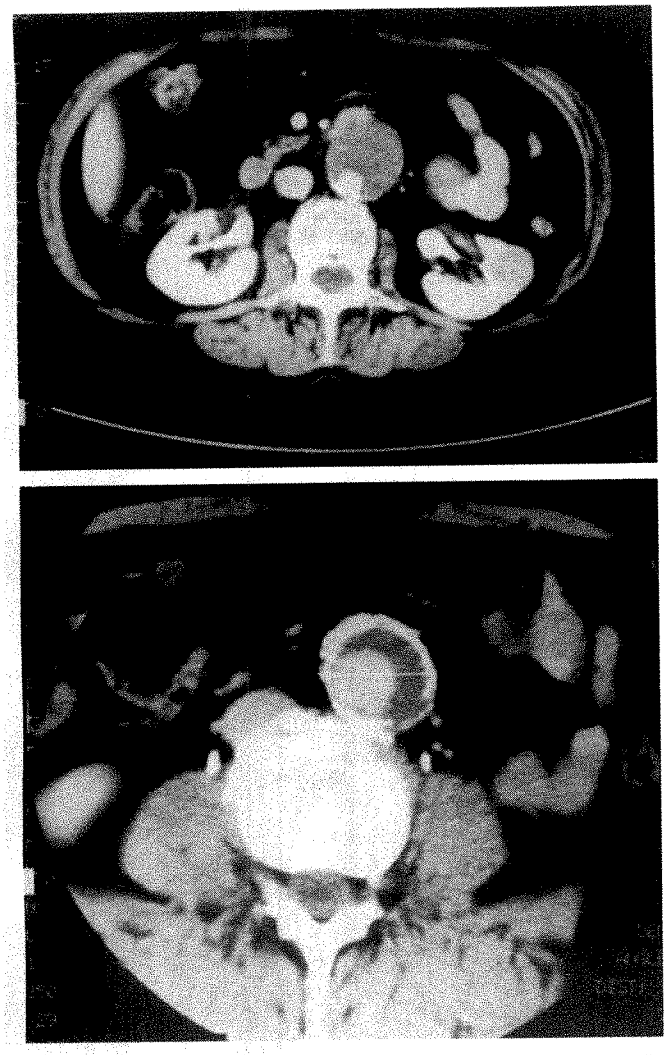

Fig 3.—Computed tomographic scans demonstrate viability in calcification. Top, Calcification occupies less than 25% of the circumference of the aneurysm and is graded 1+. Bottom, Calcification extends around the entire aneurysm and is denoted as 4+. In both instances calcium deposited is interrupted, so calcification is designated as mosaic.

Table 1.—Clinical Features*

Variable	Stable AAAs (n=11)	Expanding AAAs (n=19)	*P*
Follow-up duration, mo (range)†	21.2±4.8 (6-62)	28.9±4.1 (6-60)	NS
No. of scans (range)†	3.1±0.3 (2-6)	3.1±0.5 (2-5)	NS
Expansion rate, mm/y	0.02	4.0	<.002
Age, y†	73±3	75±2	NS
Men, No. (%)	9 (82)	16 (84)	NS
Women, No. (%)	2 (18)	3 (16)	NS
Hypertension treatment, No. (%)	6 (55)	12 (63)	NS
Systolic blood pressure, >140 mm Hg, No. (%)	5 (45)	8 (42)	NS
Diastolic blood pressure, >90 mm Hg, No. (%)	4 (36)	6 (31)	NS
Mean blood pressure, mm Hg†	155±12/93±5	145±9/83±3	NS
Coronary artery disease, No. (%)	5 (45)	12 (63)	NS
Previous myocardial infarction, No. (%)	1 (9)	8 (42)	<.05
Angina pectoris, No. (%)	4 (36)	4 (21)	NS
Peripheral vascular occlusion, No. (%)	4 (36)	6 (31)	NS
Diabetes mellitus, No. (%)	2 (18)	3 (15)	NS
Chronic lung disease, No. (%)	5 (45)	9 (30)	NS
β-Blocker treatment, No. (%)	5 (45)	10 (52)	NS
Cigarette smoking history, No. (%)	10 (90)	17 (89)	NS
Average pack-years per smoker†	52±13	46±6	NS
Serum cholesterol, mmol/L†	6.16±.38	7.90±.56	<.04
Serum triglycerides, mmol/L†	3.31±1.14	2.50±.45	NS

*AAA indicates abdominal aortic aneurysm; and NS, not significant (*P*>.05).
†Values are means±SD.

tutes of Health, Bethesda, Md. Comparisons between groups were made using Student's *t* test (two-tailed) for paired and unpaired data and the χ^2 test to determine statistical independence between groups. Variance about the mean is reported as ±1 SE.

RESULTS

Nineteen (63%) patients had enlargement of aneurysm diameter of 3 mm or more on serial CT scans, whereas 11 (37%) had little or no expansion. The majority of patients had scans repeated at 6 to 12 months, and the overall mean number of scans per patient was 3.1±0.4. Of the 19 patients with at least 3-mm enlargements, follow-up averaged 28.9±4.1 months and the mean number of scans obtained was 3.1±0.3 per patient. Those with little or no expansion were followed up for an average of 21.2±4.8 months (*P*=.24 compared with expanding abdominal aortic aneurysms) and the average number of scans obtained was 3.1±0.5 per patient. The average rate of expansion for the enlarging aneurysms was 4.0 mm/y. Stable aortic aneurysms enlarged only 0.02 mm/y (*P*=.001 compared with expanding aneurysms).

Table 1 compares the clinical features of patients with stable vs expanding aneurysms. Age and sex distributions were equivalent in both groups. Likewise, risk factors for atherosclerosis were equally prevalent. There was a trend toward more coronary artery disease in the patients with expanding abdominal aortic aneurysms, including significantly more previous myocardial infarctions. Chronic obstructive pulmonary disease or coexistent peripheral vascular occlusive disease did not correlate with aneurysm expansion. In the enlarging group, serum cholesterol level averaged 7.90±0.56 mmol/L and in the stable group it averaged 6.16±0.38 mmol/L (*P*=.03).

There was no difference in size at presentation between enlarging and stable abdominal aortic aneurysms. The mean expansion in 3.0- to 4.0-cm aneurysms was 4.7±0.2 mm compared with 5.6±0.3 mm in 4.0- to 6.0-cm aneurysms (*P*=.6). Table 2 summarizes the analysis of the CT variables studied. Size at presentation in stable and expanding abdominal aortic aneurysms averaged 4.0±0.2 cm and 4.4±0.2 cm, respectively. Likewise, aneurysm area was slightly higher in expanding than in stable aneurysms, although statistical significance was not achieved. Lumen areas and locations of the lumen were remarkably similar between groups, with ap-

Table 2.—Computed Tomographic Scan Variables*

Variables	Stable AAAs (n=11)	Expanding AAAs (n=19)	*P*
Diameter of aneurysm, cm	4.0±0.2	4.4±0.20	NS
Diameter of lumen, cm	3.4±0.3	3.3±0.5	NS
Aneurysm area, cm²	13.3±1.2	16.4±1.6	NS
Lumen area, cm²	9.0±1.2	9.1±1.1	NS
Thrombus area, cm²	4.3±0.9	7.3±0.9	.04
Thrombus-lumen ratio	0.58±0.1	1.56±0.7	NS
Thrombus-aneurysm ratio	0.32±0.1	0.43±0	NS
Lumen location, No. (%)			
Ventral	3 (28)	7 (36)	NS
Dorsal	4 (36)	6 (32)	NS
Lateral	2 (18)	3 (16)	NS
Central	2 (18)	3 (16)	NS
Calcification, No. (%)			
0+	1 (9)	0	NS
1+	6 (54)	8 (43)	NS
2+	1 (9)	4 (21)	NS
3+	1 (9)	3 (15)	NS
4+	2 (19)	4 (21)	NS
Continuous	1 (9)	2 (10)	NS
Mosaic	10 (91)	17 (90)	NS
Arc of thrombus, degrees	173.8±28.5	220.9±26.3	NS

*AAA indicates abdominal aortic aneurysm. All values, except those for lumen location and calcification, are means ± SD. NS indicates not significant.

proximately two thirds of the lumens in the dorsal or ventral position. Most aneurysms had relatively little calcification and the pattern of calcification was mosaic in 90% of cases. Thrombus area measured 7.3 ± 0.9 cm² in enlarging aortic aneurysms vs 4.3 ± 0.9 cm² in stable abdominal aortic aneurysms ($P = .04$). Ratios of T:L averaged 1.56 ± 0.7 in enlarging abdominal aortic aneurysms compared with 0.58 ± 0.1 in stable abdominal aortic aneurysms ($P = .21$), and T:A ratios averaged 0.43 ± 0.0 and 0.32 ± 0.1, respectively ($P = .17$). Arc of thrombus was somewhat greater in expanding aortic aneurysms (220.9° ± 26.3°) compared with stable aneurysms (173° ± 26.3°; $P = .23$).

Three patients (28%) died during follow-up in the group with stable abdominal aortic aneurysms. Causes of death were lung cancer, complications of hepatic cirrhosis, and respiratory arrest. One patient (5%) died during follow-up in the group with expanding abdominal aortic aneurysms. Cause of death was ruptured abdominal aortic aneurysm—the only ruptured aneurysm in this series (3%). The patient was a debilitated 82-year-old man with severe cardiac disease whose aneurysm enlarged from 5.1 to 6.0 cm over 2 years. Thrombus area in this abdominal aortic aneurysms was 7.8 cm². Two patients (18%) in the stable group underwent operative repair of 5-cm abdominal aortic aneurysms when their medical conditions had improved. Six patients (31%) eventually underwent abdominal aortic aneurysm resection for enlarging 5- to 6-cm abdominal aortic aneurysms. Thus, aneurysm repair was performed in 26% of all patients. There were no operative deaths.

COMMENT

This study reaffirms the efficacy of serial CT scans to evaluate abdominal aortic aneurysms. Size and internal architecture of aneurysms were accurately determined, and an increased amount of intraluminal thrombus correlated significantly with aneurysm expansion. Other CT variables were less predictive of aneurysm enlargement. Overall expansion rate in the 19 patients with enlarging abdominal aortic aneurysms of 0.4 cm/y is comparable with most previous studies.[5-7,10,[illegible]] Moreover, our results confirm the safety of selective nonoperative management of small abdominal aortic aneurysms in high-risk patients. Most patients were managed nonoperatively throughout the study, but 8 (27%) underwent successful aneurysm repair when size considerations or improvement in medical conditions dictated intervention. Since only one severely ill elderly patient died of ruptured aneurysm (3% incidence of rupture), the study suggests that selective application of elective aneurysm repair reduced the expected rupture rate.

The advisability of managing small abdominal aortic aneurysms nonoperatively depends on the exceptional accuracy of CT as a diagnostic modality. Although ultrasound is faster, simpler, and less expensive, it requires more skill in performance and interpretation than CT. Supplementary data about aneurysms, including proximal and distal extent, characteristics of thrombus, relationship to the renal vessels, and adjacent major veins are routinely provided by CT but not by ultrasound.[16,20] In addition, a number of investigations have reported a discrepancy between ultrasonic estimates of abdominal aortic aneurysm size and direct operative measurements.[21,22]

In contrast to ultrasound, CT scans are not hindered by observer variability, inferior images in obese or distended patients, bowel gas, or occasional inability to define aortic wall thrombus. Computed tomography is performed according to standard protocols by the instrument rather than by individuals, and results are generally easier to interpret. In addition to the CT variables we defined, CT scans can provide helpful information regarding symptomatic,[17] ruptured,[23] inflammatory,[24] and infected aneurysms.[25] Potential disadvantages to CT investigation of abdominal aortic aneurysms include radiation exposure, cost (approximately, $726 [US] per scan in our institution with a reduced price of $583 [US] for subsequent scans to define changes in aneurysm size), and the requirement for intravenous contrast.

The correlation of thrombus area with predilection for expansion of abdominal aortic aneurysms was an unexpected finding in the present study. We had thought that aneurysms with less thrombus might be subject to more tangential force, as defined by La Place's law, than aneurysms whose wall might be protected by a ring of thrombus. Likewise, we had hoped to correlate the measured thickness of the wall on CT scan with expansion rate, but found that the resolution of the CT image did not allow this determination. Finally, our original clinical impression that eccentric lumens were more prone to expansion or rupture was not corroborated by the data.

In contrast to other investigators,[10,11] we were unable to impute several clinical risk factors previously reported to predict aneurysm enlargement or rupture. In addition to lack of correlation with chronic obstructive pulmonary disease, there was no association of abdominal aortic aneurysm expansion with aneurysm size at initial presentation, coexistent peripheral vascular occlusive disease, or hypertension. Part of the explanation for the discrepancy between our findings and those of others may be due to differences in the patient populations and relative prevalence of risk factors. For example, whereas persistent diastolic hypertension was present in only one third of our patients, it occurred in half of the patients reported by Cronenwett et al[10] and Sterpetti et al.[11] Moreover, since identification of clinical features requires more individual interpretation, we prefer to establish criteria that are more operatively defined, such as the CT variables investigated.

Of those clinical features studied (Table 2), only previous myocardial infarction and serum cholesterol levels correlated with abdominal aortic aneurysm enlargement. While the first of these may be a statistical aberration (since the incidence of all manifestations of coronary artery disease was equivalent in both groups), the elevated serum cholesterol levels in patients with expanding aneurysms may be relevant. It is well accepted that increased serum cholesterol accelerates peripheral vascular occlusive disease, but there is no consensus regarding its effect on aneurysm formation or enlargement. Only much larger prospective studies can determine the importance of our finding.

Leach et al[26] postulated that β-blockade with propranolol directly increases aortic tensile strength by stimulating lysyl oxidase activity and promoting collagen and elastin cross-linking. In a retrospective study of 27 patients with small abdominal aortic aneurysms, they demonstrated a mean expansion rate of 0.44 cm/y in those not taking β-blockers compared with 0.17 cm/y in those receiving β-blockade medication ($P = .09$). Although we were unable to substantiate this finding, it is notable that a very high percentage of patients with both expanding and stable aneurysms took β-blockers (52% and 45%, respectively), and only one abdominal aortic aneurysm ruptured. In addition to its effects on collagen, β-blockade reduces pulse pressure and may be of benefit for patients with small abdominal aortic aneurysms who are believed to be poor candidates for elective resection.

Since increasing numbers of individuals with small aneurysms are being discovered, an algorithm based on the presence or absence of clinical features or objective CT variables would expedite and facilitate treatment of such patients on initial presentation. Because of the retrospective nature and limited numbers of patients in our study, we regard it as exploratory and preliminary. Since only one patient suffered a ruptured abdominal aortic aneurysm, we were unable to correlate increased thrombus area or aneurysm expansion rate with potential for rupture (although it was interesting that the ruptured aneurysm contained a large amount of thrombus). Thus, we are reluctant to manipulate our data to provide strict rules of management for small abdominal aortic aneurysms. Nevertheless, if large, prospective series corroborate our findings, the treatment of patients with asymptomatic small aneurysms may be individually tailored more precisely. In the meantime, the wide variability in abdominal aortic aneurysm expansion rates warrants frequent follow-up in patients selected for nonoperative management.

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Discussion

RONALD W. BUSUTTIL, MD, Los Angeles, Calif: Abdominal aortic aneurysms are lethal lesions—90% of patients die within 5 years of diagnosis, most due to rupture.

Surgical treatment with graft replacement has undoubtedly altered the natural history of this disease. A randomized trial is not needed. Improvements in operative, anesthetic, and perioperative care have reduced early mortality for elective resection from 20% to 2%. Sixty-three percent of those patients operated on at a median age of 66 years, survive 5 years. Survival from operation after ruptured aneurysm ranges between 40% and 70%.

Despite this overwhelming body of knowledge favoring operative repair, there recently has been an interest in identifying those patients with aneurysms who have selective indications for operation depending on their risk for rupture. In this era of cost containment and close scrutiny of indications for operations, this may be appropriate. However, identification of specific variables that define this high-risk group has been elusive and infrequently validated. These include (to name a few) presence of hypertension, chronic obstructive pulmonary disease, presence of distal occlusive disease, eccentricity of the aneurysm wall, lack of calcium and, lately, rate of expansion per year.

The rate of expansion has attracted the most recent attention and has been of keen interest to Krupski et al for a number of years. Generally, a growth rate greater than 0.5 cm/y is considered accelerated and indicative of an unstable aneurysm.

Computed tomographic scanning is the best method, to date, to diagnose and define the anatomic characteristics of abdominal aortic aneurysm. However, Krupski et al have not provided any convincing data that the thrombus area is specific for aneurysm growth or that it should influence our management of patients with small aneurysms.

The basis of my skepticism is as follows. First, this is a small prospective study of a highly selected group of patients that were considered for or excluded from surgery for a variety of reasons. Thus, their data may only be applicable to a small subpopulation of patients with aneurysms. Second, one would expect a difference in rupture rate between the expanding group of aneurysms and the stable group; however, none was found. In fact, the rupture rate was only 3% in the entire series. This, however, can be explained by the authors' correct decision to offer operation to patients with aneurysms (irrespective of stability or expansion) when the aneurysm reached 5 cm. Third, although the CT scanner used was the same model, the study spanned 10 years, during which techniques have certainly changed.

In summary, this article supports the use of CT scanning in diagnosing and monitoring aneurysm growth. However, it stops there. Until more convincing evidence is presented, I would recommend that all patients with aortic dilatation measuring 1.5 to 2 times the width of the aorta at the renal arteries be referred for operation unless there are serious medical contraindications.

Initial aneurysm size did not correlate with expansion according to LaPlace's law. Do you have an explanation for that? At what interval was the area of thrombus measured and did a change in its size correlate with change in size of the aneurysm? How would your findings affect the management of a 60-year-old good-risk patient with a 4.5-cm abdominal aortic aneurysm who had a small area of thrombus measured on CT scan? Would you operate or observe?

MAX R. GASPAR, MD, Long Beach, Calif: In 1958, Bourne and I[27] reported all aneurysms that had been seen at the Harbor-UCLA Medical Center. Most of those that had ruptured were over 7 cm in diameter, although three were found at autopsy that were under 5 cm. Since then, I have had difficulty in subscribing to the premise of operating on small aneurysms like the ones Dr Busuttil just mentioned; that is, those 1.5 to 2 times the size of the aorta just above the renal arteries. We have to consider whether we really want to remove a very small aneurysm in a frail, elderly patient.

Why does the size and the location of the thrombus have something to do with expansion? Does the thrombus interfere with the nutrition of the wall of the artery? Why does a high cholesterol level influence the expansion of the aneurysm? What do you recommend for follow-up? Are you doing away with ultrasound entirely, or do you get a basic CT scan and then follow it up with ultrasound, or do you recommend CT scans routinely, possibly at 3-month or 6-month intervals? Do you think all patients with aneurysms, expanding or not, should be receiving β-blockers?

Dr Krupski, if you had a 4-cm aneurysm, would you want it operated on, and if Dr Dilley had a 4.5-cm aneurysm, would you tell him it ought be resected? If Dr Bernstein had a 5-cm aneurysm, what would you tell him?

NEIL OLCOTT, MD, Palo Alto, Calif: You have determined the thrombus area by subtracting luminal area from aneurysm area. There is no statistical difference in aneurysm size between the two groups. Yet, when you subtract one from the other, you end up with a statistically significant difference. I am confused by the calculations.

Did you look at embolization? Perhaps an increasing thrombus area would be more important in detecting those people who are more likely to develop embolization.

KAJ H. JOHANSEN, Seattle, Wash: Thrombus forms in the context of flow turbulence, which is greater in larger and longer aneurysms. Did your CT scan data show that aneurysms with more thrombus were larger or longer, ie, did the total volume of aneurysms correlate with thrombus?

I propose that these data actually really speak to the lack of an advantage of CT scan for aortic aneurysm surveillance. The only data that you have presented that would achieve statistical significance as predicting expansion of aneurysms are the presence of previous myocardial infarction or elevated serum cholesterol levels. Neither of them can be determined by a CT scan.

I propose that, while CT scan may be valuable for studying the natural history of aneurysms in the clinical setting, B-mode ultrasound (which is noninvasive, much more rapid, one fifth as expensive, and just as accurate in following up the size change in these aneurysms) should be used.

DR BERNSTEIN: Around 1970, ultrasound showed us the size of an aneurysm accurately in vivo. All the data prior to 1970 relating aneurysm rupture and size were from autopsies.

Ultrasound taught us about aneurysm expansion rates. We began to learn the mean expansion rate and the variation among individuals. With ultrasound we found an extraordinarily large number of people with small aneurysms. Eighty percent of the aneurysms diagnosed are now smaller than 6 cm. Computed tomography came a decade later and is better, although it is more expensive, because it tells us about para-aneurysmal disease such as kidney tumors, pancreatic lesions, etc; CT data about aneurysm size are objective and anybody can interpret them with equal accuracy. Because of the cost factor, if your ultrasound is reliable, it is a good method for following up patients with aneurysms. On the other hand, CT is more precise and objective.

One has to consider this a pilot study. What does the relative amount of thrombus mean for expansion rates of aneurysms? We are not sure.

When you look at several hundred aneurysm interiors in the operating room, they differ markedly. Some are gel-like; some are liquefied and necrotic. Some have more structure and some less. I wonder if this so-called thrombus has something to do with collagen and elastin digestion. Maybe the so-called mural thrombus is an end product that is a measure of how rapidly these enzymes are working on the wall. The "thrombus" may be secondary to a primary change in the geometry of the wall, and that is a flow factor phenomenon, not a chemical one.

There was a trend to more rapid rates of expansion in patients with large aneurysms but not a big trend, and the mean expansion rates of aneurysms that are 5 or 6 cm were not terribly different from those of 4 cm.

Regarding your question about the 60-year-old healthy man with a 4.5-cm aneurysm and small thrombus, that is about my borderline. I have become progressively more aggressive with time, because we now have an elective mortality rate of 1% and a 5-year survival rate of approximately 80%, which approaches the normal population of the same age and sex. I would talk with that patient at greater length than with the average patient. I would give him all the pros and cons of morbidity and mortality and I would tell him that we can get his aneurysm repaired quickly and easily with very low risk, but on the other hand, I cannot tell him that he really is at high risk of death from rupture. I would assume that if he did not want it operated on now, he would come back in 6 months or a year when it was 5 cm, when it would be much easier for me to convince him to have it operated on.

We prefer to use CT scanning for both the original diagnosis and follow-up despite the cost, although in other institutions ultrasound might be preferable. If we elected not to operate primarily because of a patient's poor risk, we would see that patient every 3 months.

We do not use β-blockers. David Tilson has stimulated a prospective, multicenter, randomized study on the use of β-blockers in aneurysm expansion and such data will be available in the near future.

Dr Johansen, we have no data about length of aneurysm, and this is an important area to study. I know of no such data in the literature.

Treatment of Traumatic Rupture of the Thoracic Aorta

A 15-Year Experience

A. Craig Eddy, MD; Valerie W. Rusch, MD; Thomas Marchioro, MD; David Ashbaugh, MD; Edward D. Verrier, MD; David Dillard, MD

• Traumatic rupture of the thoracic aorta is increasing in incidence and remains a highly lethal injury. The morbidity associated with this injury also remains high. We retrospectively reviewed the records of all patients admitted to our emergency department with ruptured thoracic aortas during a 15-year period to determine the reason for this persistently high morbidity and mortality and to identify any factors that might improve the outcome. We found that patients who are in unstable condition on arrival in the emergency department or who become unstable before reaching the operating room are not likely to survive. Patients who are injured in automobile accidents have a greater chance of survival than do those injured in motorcycle accidents or car-pedestrian accidents. Patients who are in hemodynamically stable condition after aortic injury survive only if diagnosis and treatment are prompt. Major complications of repair following thoracic aortic injury relate primarily to the length of cross-clamp time, and every effort should be devoted to keeping the cross-clamp time less than 30 minutes.

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Rupture of the thoracic aorta (RTA) following blunt thoracic trauma frequently is a lethal injury that has been well characterized epidemiologically in both adults and children.[1-5] It has been associated with many different types of sudden-deceleration injury, including car and motorcycle accidents, falls, airplane and train accidents, skiing and equestrian mishaps, blast injuries, and cave-ins.[2,5,6] Several investigators have shown that RTA occurs in 10% to 30% of adults sustaining fatal blunt trauma and found that it is one of the most common causes of death at the scene of a motor vehicle accident.[1,2,7,8]

Because most serious blunt thoracic injury is secondary to traffic accidents, and over the past three decades high-speed automobile travel has increased, it is not surprising that the incidence of RTA has also increased during this interval.[9] Furthermore, more sophisticated prehospital care and the proliferation of rapid patient transport systems, especially helicopters, has increased the number of patients with RTA who survive to reach the hospital.[10-12] The morbidity and mortality associated with this injury, however, remain high, even among those patients who reach the hospital.[5,13,14] The purpose of this review was to determine the reason for this persistently high morbidity and mortality among patients who survive to reach the hospital and to identify any factors that might improve the outcome.

MATERIALS AND METHODS

We retrospectively reviewed the emergency department (ED) and operating room (OR) records at a major university trauma center for 15-years from January 1975 to August 1989. Patients who arrived in the ED alive and subsequently diagnosed either before or after death as having RTA were identified, and their medical records, autopsy data, and police accident reports were reviewed in detail. The following characteristics were noted: (1) age, (2) sex, (3) mechanism of injury, (4) presence of hemodynamic instability, (5) method of diagnosis, (6) time from injury to diagnosis and repair, (7) site and extent of aortic tear, (8) method of repair or attempted repair, (9) method of distal perfusion (if used), (10) cross-clamp times, (11) complications, (12) associated injuries, and (13) cause of death as established by the medical examiner. Hemodynamic instability was defined as sustained blood pressure less than 90 mm Hg despite adequate fluid resuscitation. Data were contrasted using χ^2 analysis, Fisher's Exact Test, Student's t test, and Kruskal-Wallis one-way analysis of variance. $P<.05$ was considered statistically significant.

RESULTS

We identified 104 patients who survived RTA long enough to reach the ED. Their median age was 31 years, and 81% were male. Mechanisms of injury (Table 1) included automobile accidents, motorcycle accidents, car vs pedestrian accidents, and falls. Victims of automobile accidents were significantly more likely to survive RTA than were victims of motorcycle accidents or car-pedestrian accidents ($P<.05$). Among the 74 automobile accident victims, only one was noted to be wearing safety restraints. Sixty-three automobile accidents occurred at high speed.

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Table 1.—Mechanism of Injury and Its Effect on Mortality Following Blunt Thoracic Aortic Injury

Mechanism of Injury	Total No. of Patients	No. (%) of Survivors
Motorcycle accidents	18	6 (33)
Car-pedestrian accidents	8	1 (12.5)
Falls	4	2 (50)
Automobile accidents*	74	36 (48)

*Among the automobile accident victims, 59 (80%) were drivers, 12 (16%) were front-seat passengers, and three (4%) were rear-seat passengers. Victims of automobile accidents are statistically significantly more likely to survive than are those of motorcycle or car-pedestrian accidents ($P<.05$).

Table 2.—The Effect of Hemodynamic Instability on Survival Following Aortic Injury*

	No. of Patients
Hemodynamically unstable patients	
Died in ED with thoracotomy	16
Died in ED without thoracotomy	15
Died in OR after thoracotomy in ED	10
Became unstable before angiography	10
Survived operation after thoracotomy in ED	1
Left the hospital alive	1
Hemodynamically stable patients	
Underwent angiography	52
Died after angiography before repair	1
Died in OR	7
Survived operation	44
Died in hospital of causes other than aortic injury	4
Left hospital alive	40

*Hemodynamically unstable patients includes those who arrived in the emergency department (ED) in hemodynamically unstable condition and those who became unstable before angiography. Survival after thoracic aortic injury is statistically significantly lower ($P<.001$) in patients who are hemodynamically unstable compared with those who are hemodynamically stable (2% of hemodynamically unstable patients survived aortic repair [98% mortality] vs 85% of hemodynamically stable patients [25% mortality]). OR indicates operating room.

Table 3.—Location of Aortic Injuries*

Location	No. (%) of Injuries Observed	No. (%) of Survivors
Ascending aorta	0	. . .
Aortic arch	7 (7)	2 (29)
Ligamentum arteriosum	93 (87)	42 (45)
Descending thoracic aorta	6 (6)	1 (16)
Multiple site	2 (2)	0 (0)

*Values are for 106 injuries seen in 104 patients who survived to reach the emergency department; two patients had multiple injuries.

Among the 104 patients who initially survived aortic injury, 42 died before the injury was diagnosed or repair could be attempted. In all 42 of these patients, aortic transection was listed as a cause of death by the medical examiner. Sixty-two patients underwent attempted repair, and 17 patients died before the repair was completed. In all cases, aortic transection was listed as a cause of death by the medical examiner. Forty-five patients underwent successful repair, and 41 survived to leave the hospital. Four patients died after successful aortic repair of complications of other injuries, with head injury being the most common.

Premortem diagnosis was made in 89 patients, and diagnosis was made at autopsy in 15 patients. Aortic injury was identified by thoracotomy in the ED in 37 patients and by arteriography in 52 patients. In five of the 52 patients, aortic injury was diagnosed by digital subtraction angiography. Only one (3%) of the 37 patients whose injury was diagnosed by thoracotomy in the ED survived repair compared with 44 (84%) of the 52 patients whose injury was diagnosed by arteriography ($P<.001$).

Among the 42 patients who died before aortic repair could be attempted, 16 underwent immediate thoracotomy in the ED and unsuccessful resuscitation. Ten patients were initially in stable condition but became unstable within 1 hour and subsequently underwent thoracotomy in the ED and unsuccessful resuscitation. Fifteen underwent an unsuccessful resuscitation in the ED without thoracotomy less than 1 hour after injury and subsequently were found to have unsuspected RTA at autopsy. One patient experienced cardiac arrest and died following diagnostic aortography before reaching the OR. Thus, 31 patients in this group of 42 arrived in the ED in hemodynamically unstable condition and could not be resuscitated. Eleven patients were hemodynamically stabilized initially but died of aortic injury before attempted diagnosis or repair. Reasons for delay in diagnosis included treatment of higher-priority or more immediately life-threatening injuries in eight patients and free rupture before angiography was performed in three patients.

Sixty-two patients underwent attempted operative repair, 11 of whom were in hemodynamically unstable condition and in whom diagnosis was made by thoracotomy in the ED. These patients were taken directly to the OR for attempted repair, but only one patient in this group survived. Among the 62 patients who underwent attempted operative repair, 51 had undergone diagnostic arteriography. Of these, 44 patients survived aortic repair.

The influence of hemodynamic instability is summarized in Table 2. Patients who present to the ED in hemodynamically unstable condition or become hemodynamically unstable before surgery are significantly less likely to survive their injury than are patients who remain in stable condition ($P<.001$).

Among the 52 patients in sufficiently stable condition to undergo arteriography, survival decreased with delay in diagnosis. Overall, 44 patients survived the operation. One patient died during transfer to the OR and seven died in the OR. Twenty-nine (94%) of 31 patients whose RTA was angiographically diagnosed less than 3 hours after injury survived surgery, whereas only 15 (71%) of 21 patients whose diagnosis was delayed more than 3 hours survived surgery. This approached but did not reach statistical significance ($P=.08$).

The locations of aortic injuries are summarized in Table 3. Rupture at the ligamentum arteriosum accounted for the majority (87%) of all injuries. Survival following RTA varied with the location of the aortic injury. Overall, 28% of patients with injuries to the aortic arch, 45% of patients with injuries at the ligamentum arteriosum, and 17% of patients with injuries to the descending aorta survived. No patient with multiple aortic injuries survived operation. Among the 52 patients who were in sufficiently hemodynamically stable condition to undergo arteriography, 41 (89%) of 46 patients with injuries at the ligamentum arteriosum survived compared with three (50%) of six with injuries in the arch or descending aorta; this was not statistically significant ($P=.11$).

The injuries most commonly associated with RTA are listed in Table 4. Survival varied inversely with the number of associated major injuries. Patients who died had an average of 4.0 associated injuries compared with 2.6 in survivors.

Among the 62 patients taken to the OR, 17 did not survive

Table 4.—Injuries Most Commonly Associated With Aortic Injury*

Injury	No. of Nonsurvivors (n=59)	No. of Survivors (n=45)
Open cardiac injury	11	0
Closed cardiac injury	14	5
Great-vessel injury	5	1
Head injury	35	17
Spinal injury	11	4
Pulmonary injury	30	25
Chest-wall injury	41	20
Abdominal injury	46	13
Pelvic fracture	16	9
Extremity fracture	30	23

*There was an average of 4.0 injuries in nonsurvivors and 2.6 injuries in survivors.

Table 5.—A Comparison of Complications Following Repair of Traumatic Aortic Rupture Based on the Use of Distal Aortic Perfusion*

Complication	Without Distal Perfusion (n=26)	With Distal Perfusion (n=19)
Paraplegia	3	4
Paraparesis	2	2
Renal failure	2	1
Pneumonia	5	4
Arrythmia	4	2

*There was no statistically significant difference in the incidence of complications based on the use of distal perfusion. Values represent numbers of patients.

Table 6.—A Comparison of Complications Following Repair of Traumatic Aortic Rupture Based on Length of Aortic Cross-Clamp Times

	No. of Patients by Aortic Cross-Clamp Time, min		
Complication	<30 (n=9)	30-45 (n=15)	>45 (n=21)
Paraplegia*	0	2	5
Paraparesis*	0	1	3
Renal failure	0	1	2
Pneumonia	2	4	3
Arrythmia	2	3	1

*The incidence of spinal cord ischemia increased significantly with cross-clamp times greater than 30 minutes ($P<.05$).

surgery. Ten of the 17 deaths occurred in patients who had undergone resuscitative thoracotomy in the ED for severe hemodynamic instability. In 18 patients, proximal aortic control was never achieved. In two patients, interposition grafts were placed only after massive blood loss, and they subsequently suffered cardiac arrest during unclamping of the aorta. Seven of the 17 deaths occurred in patients who had undergone arteriography. In three patients, proximal aortic control was never achieved. In the remaining four patients, an interposition graft was placed, but the patients suffered cardiac arrest and died during or after aortic declamping.

Among the 45 survivors, 36 patients underwent aortic repair with use of an interposition graft, four were repaired with a patch, and five underwent primary repair. In 26 patients, repair was performed without distal aortic perfusion and in 19 repair was performed with distal perfusion. The decision whether to employ distal aortic perfusion was made by the individual surgeon at the time of the operation and was based on the condition of the patient and the surgeon's preference. Perfusion was accomplished with the use of several methods, including an aorto-aortic Gott shunt (n=8), full cardiopulmonary bypass (n=2), left ventricle to distal aortic shunt (n=1), and left atrial to distal aortic shunt with use of a heparinless pump (n=8). Distal aortic pressure was not routinely monitored by lower-extremity pressure monitoring. Aortic cross-clamp times averaged 35 minutes (range, 18 to 56 minutes) in patients without distal bypass and 59 minutes (range, 32 to 90 minutes) in patients in whom distal bypass was performed. Aortic cross-clamp times were significantly shorter in patients in whom shunts were not placed ($P<.001$).

The incidence of major complications following aortic repair is presented in Tables 5 and 6. Paraplegia and paraparesis together make up the spectrum of spinal cord ischemia. The incidence of major complications, particularly spinal cord ischemia, was not statistically related to the use of distal bypass (Table 5). Aortic cross-clamp times ranged from 18 to 90 minutes, and the incidence of spinal cord ischemia increased significantly ($P<.05$) with cross-clamp times greater than 30 minutes (Table 6).

COMMENT

The number of patients seen in EDs found to have traumatic rupture of the thoracic aorta is increasing and presents a continued challenge to the thoracic trauma surgeon. In our review, it is striking that only one of the more than 100 patients who arrived in the ED alive was wearing a safety restraint and that the majority of accidents occurred at high rates of speed. It seems reasonable to conclude that the use of safety restraints may decrease aortic injury in survivors of high-speed automobile accidents.

We found that patients in hemodynamically unstable condition were significantly less likely to survive their injuries than were those patients whose condition was stabilized with fluid resuscitation. This is in disagreement with the observations of Sturm et al,[15] who retrospectively reviewed the course of 37 patients found to have RTA and concluded that the presence of hypotension on admission had no bearing on survival. This disparity has probably occurred for two reasons. First, we included in our series all patients who survived to reach the ED, whereas the patients described by Sturm et al were preselected and included only those patients who survived long enough to undergo diagnosis and surgery. Second, underlying these disparate conclusions may be that the two studies differ in their definition of hemodynamic instability. The criteria set forth in our study are relatively strict (blood pressure <90 mm Hg despite adequate volume resuscitation) compared with the criteria established by Sturm et al (a single blood pressure measurement of <100 mm Hg in the ED). Our definition of hypotension seems preferable based on our observation that many trauma victims, including patients who have sustained relatively minor injuries, present to the ED with an isolated blood pressure measurement less than 100 mm Hg but generally respond quickly to moderate volume resuscitation and remain in stable condition thereafter.[16] We conclude that marked hemodynamic instability is a poor prognostic sign in thoracic aortic injury.

During the past few years, many trauma surgeons have questioned the efficacy of thoracotomy in the ED in the resuscitation of blunt trauma victims. Bodai et al[17] and Hoyt et al[18] concluded that resuscitative thoracotomy added no benefit to survival in blunt trauma victims. Our data strongly confirm this concept. Thirty-seven patients underwent thoracotomy in the ED, but only one patient survived (97% mortality). Furthermore, on retrospective review of the survivor's chart, it is unclear whether resuscitative thoracotomy was necessary. We conclude that resuscitative thoracotomy is fruitless in patients in hemodynamically unstable condition with RTA.

Several authors have commented on the increase in the number of thoracic aortic injuries seen in EDs and have speculated that this has been due in part to improved prehospital care and faster methods of patient transport.[9-12] Such speculation is difficult to prove because of the problems presented by retrospective review of prehospital and inpatient records. At our institution, a trauma registry has been in place for the past 3 years in which data, including the hospital and prehospital care and outcome of traumatic injuries, are prospectively recorded. It is clear from these records that the acuity of injury among patients in the ED has increased during this time. Nonetheless, it is not possible to ascertain the relative contribution of prehospital care and improved patient transport to this trend. While it may well be true that many patients are now surviving to reach the ED but would have died of their injuries in the field previously, this does not necessarily imply a corresponding improvement in the outcome of a particular injury. In our series, only 2% of patients who were in hemodynamically unstable condition on arrival in the ED or in whom hemodynamic instability developed within 1 hour of their arrival survived compared with a 75% survival rate among patients in sufficiently stable condition to undergo arteriography. Therefore, patients who sustain RTA and who survive to reach the ED may now represent a less "salvageable" group in light of improved capabilities to transport and/or transiently stabilize severely injured patients and those in hemodynamically unstable condition.

Our data strongly underline the importance of expeditious diagnosis in improving survival. The difference in mortality among patients whose injury was diagnosed early (<3 hours after injury) vs late (>3 hours after injury) approached but did not achieve statistical significance. The trend toward decreased survival in the group of patients in stable condition who underwent attempted repair more than 3 hours after injury may best be explained by increasing technical problems related to an expanding aortic hematoma. As the aortic hematoma expands with time, normal intrathoracic anatomy is distorted and the size of the intimal disruption may increase and extend proximally into the aortic arch. These factors combine to make proximal aortic control more difficult. Among the six intraoperative deaths in our series that occurred in patients who underwent angiography but whose attempted repair occurred more than 3 hours after injury, adequate proximal control before cardiac arrest was not achieved in three and was associated with a large blood loss in two others.

Furthermore, 11 patients were in stable condition on arrival in the ED but subsequently died of free intrapleural aortic rupture. It is possible that these patients might have survived their injuries if RTA had been identified more rapidly and operative repair had been attempted before hemodynamic instability occurs. Intravenous or intra-arterial digital subtraction angiography can decrease the length of time required for identification of aortic injury.[19,20] The use of these or other modalities to evaluate patients with potential RTA should be considered.

Although the location of aortic injury did not correlate statistically ($P<.11$) with survival, there was a strong trend toward enhanced survival among patients with tears at the ligamentum arteriosum. Because traumatic aortic rupture at sites other than the ligamentum arteriosum are rare, few surgeons have experience in the repair of these injuries. In addition, ruptures involving the aortic arch present the greatest technical challenges to proximal aortic control and repair.

The incidence of spinal cord injury complicating thoracic aortic cross-clamping has been reported to be as high as 24% or more.[21] Although the mechanism of the spinal insult is clearly ischemia or ischemia-reperfusion, the factors that influence and modify this complication are not well defined.[22-26] Although evoked potentials were not used in our patients to detect subtle spinal cord ischemia, our study clearly demonstrates that the likelihood of major spinal cord damage is increased by relatively prolonged aortic cross-clamp times. In our series, no ischemic spinal cord injuries were observed postoperatively when the aortic cross-clamp was in place less than 30 minutes. The incidence of spinal cord ischemia was 20% after cross-clamping lasted 30 to 45 minutes and jumped to 38% in cases in which cross-clamping lasted longer than 45 minutes. Therefore, it is imperative to make every effort to minimize aortic cross-clamp times.

The utility of distal perfusion in reducing spinal cord ischemia during aortic repair remains controversial. Some authors have strongly advocated the use of distal bypass, while others have stated that repair without bypass is clearly the procedure of choice.[27-29] The difficulties inherent in distal bypass are primarily the logistics of placing the shunts and the increased complexity of equipment cluttering the operative field. It has been argued that these factors alone may prolong aortic cross-clamp times and offset any potential benefits conferred by distal perfusion. Proposed benefits are protection from spinal cord,[30] renal,[31] and hepatic[32] ischemia during aortic cross-clamping. Our study shows no difference in the incidence of spinal cord injury or renal failure after aortic clamping with or without distal bypass procedures. We have reported previously that the metabolic derangements induced by hepatic ischemia are more severe after simple cross-clamping compared with cross-clamping with bypass.[32] However, we noted that by anticipating and appropriately treating these derangements at the time of cross-clamp removal, the relative increase in ischemia did not adversely affect morbidity and mortality. In fact, in a small series[32] of eight patients seen in a single year, there were no spinal cord injuries among patients operated on without distal aortic perfusion and two cases of paraplegia among patients with perfusion.

In the absence of conclusive evidence that distal aortic perfusion is beneficial, the widespread use of this technique may be surprising. Unfortunately, in the United States, the medicolegal ramifications of aortic injury can affect our judgment as surgeons. Because traumatic aortic ruptures occur primarily in young adults, the consequences of paraplegia in terms of lost productivity are particularly devastating. In today's legal climate, this has translated into the possibility of large monetary awards to aortic trauma victims who become paraplegic even if it cannot be clearly established that distal aortic bypass reduces this complication.

These complex issues raise the question as to when distal aortic perfusion should be considered and by what method. We believe that this is a surgical judgment that must be made at the time of operation. In patients who have straightforward aortic tears without arch involvement and who present in the OR with small localized hematomas, repair without distal perfusion is the most rapid and expeditious method for repair. However, in patients with more extensive injury and complex anatomy, we may consider the use of some form of distal perfusion. We have tried several different techniques for distal perfusion, including the Gott shunt, left ventricle to aorta shunt, heparinized full cardiopulmonary bypass, and heparinless left atrial to distal aorta shunt. Most trauma victims with aortic tears have multiple injuries, so heparinization should be avoided. In addition, the ideal method of distal bypass must be simple to employ and should not prolong cross-clamp times. Distal perfusion with the heparinless vortex centrifugal pump has recently gained popularity.[33,34] If distal aortic perfusion is judged to be necessary by the operating surgeon, we have found this to be a very satisfactory method. We employ a right-angle cannula in the left atrium, which can be directed out of the operative field. If the aortic hematoma is relatively small, a distal thoracic aortic site can be used for the arterial cannulation site and the arterial line routed anterior to the hilum out of the surgical field. If the hematoma is large, the femoral artery can be used for the cannulation site, again out of the surgical field. Bypass is initiated before dissection of the aortic hematoma in an attempt to decrease the risk of intraoperative aortic rupture before proximal aortic control. The advantages to this type of distal bypass are that it not only accomplishes oxygenated perfusion of the distal aortic bed but also decreases proximal hypertension associated with aortic clamping and decreases left ventricular afterload. The degree of afterload reduction can be varied by altering the flow from the pump. These factors often greatly simplify the anesthetic management of the patient.

The decision about how to repair the aortic injury remains with the individual surgeon. Primary repair has many advantages over repair with a prosthetic graft or patch and can be accomplished safely in many cases.[35,36] However, the most important consideration is that regardless of the method, the repair needs to be completed safely in less than 30 minutes. Therefore, a rapid, accurate assessment of the injury after the aorta has been exposed is the most critical step. It is disastrous to begin a primary repair only to realize later that a graft is necessary and that the repair must be repeated. For this reason, we would place an interposition graft if there is any question about whether a primary repair can be accomplished.

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Discussion

RONALD J. NELSON, MD, Santa Monica, Calif: Since 1958, it has been widely recognized that approximately 85% of patients with traumatic rupture of the aorta die before reaching the hospital. Efforts to improve this dismal record have centered on prevention on the one hand and on more expeditious care on the other. As a society, we still need to concentrate on prevention to significantly decrease the number of these unfortunate deaths.

As surgeons, we will have a greater influence in promoting the design of cars that absorb the force of impact, in promoting the mandatory use of seat belts and air bags, and in campaigning for safer roadways and driving laws.

With improved prehospital care and rapid evacuation, more blunt trauma victims are arriving in the ED alive, but the small number of survivors with aortic rupture is lower. Even at Harborview Medical

Center, Seattle, Wash, emergency thoracotomy was unproductive—only one survivor in 42 attempts—in keeping with the experiences of other centers. There was a glimmer of hope for the 11 patients whose conditions were initially stabilized, had the diagnosis been made and control established in less than 1 hour. Rapid digital subtraction angiography with intravenous dye, if possible, may be the best hope. What are the authors' indications for this study, and how quickly can it be accomplished?

In those victims whose condition is too unstable for even rapid digital angiography, is there a role for the percutaneous life support systems now being developed, particularly if improved heparin bonding proves feasible?

After hypotension is controlled, hypertension is often a problem, probably due to stimulation of the rich sympathetic plexus in the adventitia, and may be a clue to the diagnosis. Control of this hypertension with nitroprusside, or judicious use of short-acting β-blockers, may be very important. We have a house officer in constant attendance monitoring the patient and managing this internal therapy.

To what degree could the deaths be attributed to causes other than the ruptured aorta? These patients are indeed an exercise in multisystem management. How many different operating surgeons were involved during the 15 years of this review? A cross-clamp time of less than 30 minutes does not guarantee absence of spinal cord damage; however, the relationship of cross-clamp time to incidence of paraplegia is in keeping with the experience of many others. I, too, avoid the use of shunt placement, unless the injury is complex, and favor direct repair when the tear is not circumferential. It is true that shunt placement in the field carries its own risks in this series. I, too, favor the use of the centrifugal pump if needed and always call the pump team in on a standby basis.

CARLOS SCHMIDT, MD, Loma Linda, Calif: At Loma Linda, we have had a very similar experience with similar results.

Different types of repairs, such as bypasses and shunt placement, have not changed the outcome. The only thing that appears to change the morbidity and the mortality is the cross-clamp time. To decrease cross-clamp time, we have been able to do primary repair on most ruptured aortas. By doing a primary repair, we have cut down the average cross-clamp time to about 12 minutes in all patients. The last 32 consecutive aortic ruptures have been repaired primarily.

How many patients in this series received grafts, and how many underwent primary repair?

We have noted a tremendous decrease in the number of aortic ruptures since the seat belt laws have been instituted in California. Is this true in Seattle as well?

WILEY F. BARKER, MD, Los Angeles, Calif: One can find several reports in the orthopedic literature that focus on major trauma and fracture of the spondylitic thoracic spine and an associated classical rupture of the thoracic aorta. There is usually some surprise expressed at finding rupture of the thoracic aorta in these patients, and treatment of the aortic lesion is at times delayed. Paraplegia is usually attributed solely to the fracture of the spine, and distal ischemia, especially in the presence of shock, is passed over lightly. It is commonly suggested that the aorta may rupture because of an associated aortitis related to the disease that caused the spondylitis. It is implied that rupture of the aorta is uncommon, except in the presence of a fractured thoracic spine. Have the authors encountered this phenomenon? How commonly is aortic rupture and a fracture of the spine, spondylitic or otherwise, seen?

DR DILLARD: The most interesting new finding is that of patients who come into the hospital "alive"; many have been resuscitated in the field. In general, if the patient arrives at the hospital dead, he tends to stay in that state, and emergency thoracotomy is a disaster without salvage. A prompt and orderly workup of the patient with the use of angiography and transfer to the hospital OR does make a difference, as the data show. We have used digital subtraction studies. They can be done rapidly but do not absolutely rule out a rupture, so we have relied on angiography as the "gold standard."

There were five different surgeons involved in this 15-year study.

Shunt placement increases the risk of problems and of a prolonged cross-clamp time, so many of us prefer to pursue the more rapid direct repair.

We have occasionally seen patients who seem to be paraplegic because of spinal cord injury, but we cannot attribute the paraplegia to this if the patient has also had an operation for a ruptured aorta. Among the 51 repairs in our series, there were four patches and five primary repairs; the remainder were interposition grafts. I am surprised at the high incidence of primary repairs reported by some authors. Our experience has been that if the tear is circumferential, the two ends are widely separated, and bringing them together is very difficult. If one attempts this and then has to revert to an interposition graft, the cross-clamp time is substantially prolonged. We do do primary repair when the tear is not completely circumferential; otherwise we employ an interposition graft.

Blood pressure is usually controlled with short-acting β-blockers, with careful monitoring before and during the operation.

Angioscopy for Intraoperative Management of Thromboembolectomy

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• Our experience with angioscopy suggests that direct visualization of the arterial lumen during thromboembolectomy procedures would provide a more reliable method of assessing luminal morphologic characteristics than angiography alone. We inspected 32 grafts (seven aortobifemoral, 18 infrainguinal bypass, and seven dialysis access fistula grafts) in 32 patients. Thirty-one patients had thrombotic events and one patient had an acute embolus. Angioscopy following standard catheter thrombectomy revealed significant amounts of retained thrombus or neointima in all thrombectomies. Angioscopic information from 18 patients with an infrainguinal bypass graft led to graft revision in six cases and placement of a new graft in 10 cases. One graft limb was replaced in seven aortobifemoral grafts, and multiple repeated thrombectomies were employed to extract debris in the remaining six cases. Repeated graft thrombectomy was also beneficial in dialysis access fistulas. Angioscopy allowed us to omit the completion angiogram and led to an improved technical result. We conclude that angioscopy is useful during thromboembolectomy procedures.

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Our group has previously described the techniques of intraoperative angioscopy for delineation of luminal morphologic characteristics.[1] Subsequent efforts demonstrated the ability of angioscopy to identify an intraluminal thrombus not well defined by angiography.[2] In our initial experience, angioscopy after initial thrombectomy revealed extensive retained thrombus and luminal filling defects in six of seven cases. However, in this experience, angioscopic techniques were limited by lack of appropriate instrumentation. Visualization of the lumen was achieved only after cumbersome irrigation displaced blood from the field, and assembly of angioscopic systems was often time-consuming.[3] Over the last 3 years, in collaboration with several manufacturers, we have refined our angioscopic techniques, permitting reliable visualization of the lumen in thrombus-filled arteries or grafts. Our experience and the experience of Mehigan and Olcott,[4] White et al,[5] and Miller et al[6] suggest that angioscopy might be valuable when angiography is difficult to perform or interpret.[7] Thus, angioscopy might permit the surgeon to perform thrombectomy with greater control and less residual thrombus. The goal of this study is to assess the role of angioscopy during thrombectomy.

PATIENTS AND METHODS

Methods

We used angioscopes from four manufacturers: Olympus (Lake Success, NY), Baxter-Edwards (Irvine, Calif), Karl Storz (Culver City, Calif), and Intramed Laboratories (San Diego, Calif). Each manufacturer provided its own endoscopic system.

The Olympus system employed angioscopes 0.8, 1.4, 2.2, and 2.8 mm in diameter. The angioscopes were coupled to a modified solid-state video camera. Images were displayed on a high-resolution color monitor. Irrigation was provided by an Olympus roller pump designed to our specifications for angioscopic applications.

The Baxter-Edwards system was modified during the study. Although angioscope size was not altered, significant improvements were achieved in image resolution and ease of use. The system employs reusable endoscopes 0.85 and 1.0 mm in diameter placed inside 5F or 7F guide catheters. In 1988, Baxter-Edwards introduced a 2.3-mm disposable angioscope with 6000 pixels in the imaging bundle. This angioscope contains its own 1.0-mm irrigation channel and couples directly into a solid-state video camera. The resulting image is displayed on a 35-cm high-resolution monitor (Sony, New York, NY).

The prototype Storz angioscope contained a high-resolution image bundle and a 1.0-mm irrigation channel coupled to a standard solid-state video camera with antiblooming circuitry. The Intramed system employs three different angioscopic catheters 0.7, 2.1, and 2.8 mm in diameter. These disposable angioscopes are coupled to a high-resolution solid-state video camera (Panasonic, Secaucus, NJ) and a monitor (Sony). The 2.1- and 2.8-mm devices can be actively steered in one direction and contain a 1.0-mm working channel.

Illumination is provided by a 300-W xenon light source supplied by the above manufacturers. Each light source is different in construction and is designed to deliver light into a specific optical coupler. Although it is possible to interchange light sources through the use of adapters, this tends to decrease coupling efficiency and leads to suboptimal illumination. Automatic gain control and illumination feedback control circuits, although available in some models, were not useful. Failure of automatic gain control circuitry to improve the angioscopic image was due in large part to the projection of a relatively small image onto a large monitor screen. In the presence of an automatic gain control circuit, only a small portion of the visual field is lighted by the small angioscopic image; thus, the gain always operates at maximum. In addition, angioscopic light requirements tend to fluctuate rapidly as the angioscope is directed at white or red walls or the central lumen. Therefore, manual control of illumination was preferable. The introduction of antiblooming circuitry and cameras with improved dynamic range has improved image quality. The presence of a skilled technician simplifies use of the equipment but is no longer required, as newer systems are easier to operate.

In all cases an angioscopy system operator was present to provide consistent operation of the equipment and interpretation of the images as well as precise data collection. The presence of a trained system operator permits rapid archiving of the data and improves the longevity of the angioscopes. Choice of angioscope was based on the availability of instrumentation and the size of the blood vessel to be inspected. The diameter of the angioscope was less than two thirds

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the diameter of the blood vessel. Careful selection of the angioscope is essential to prevent injury to the arterial or graft wall. Normal saline was used for fluid irrigation and was delivered to the site of inspection either through the angioscope itself (if a channel was present) or via a coaxial irrigation catheter. When dealing with native arteries, an introducer sheath is employed to prevent damage to the arteriotomy wall, and the side port can be used for irrigation. In all cases, initial irrigation was performed to clear the lumen. In the blood vessel to be inspected, flow rates of 50 to 125 mL/min were initially provided; rates were decreased to 10 to 75 mL/min to maintain a clear visual field. The total volume infused (not necessarily into the patient) rarely exceeded 500 mL, and no clinical sequelae occurred as a result of fluid infusion.

Intraoperative Techniques

Using standard surgical approaches, the artery or graft to be thrombectomized was isolated and controlled. In 32 patients, angioscopy was used to assess the nature and location of the obstruction before a Fogarty thrombectomy catheter was introduced. Thrombectomy was performed in a standard fashion using a Fogarty catheter passed beyond the obstruction. Balloon inflation and debris extraction was repeated until no further thrombus was found. Following thrombectomy, angioscopy was used to identify residual thrombus, neointimal hyperplasia, neointimal flap, retained valves, and other luminal obstructions. Identification and localization of residual debris permitted angioscopically directed thrombectomy. In two cases, an Olympus pulmonary brush was employed to extract residual thrombus and neointimal debris from grafts. With angioscopic control, the Fogarty balloon catheter was positioned and inflated. After thrombectomy, inspection of the distal outflow tract was performed by observing retrograde blood flow distal to the site of thrombectomy.

Patients

From September 1, 1987, through August 31, 1989, angioscopically guided Fogarty catheter thromboembolectomy was performed on 32 patients with occluded arteries or grafts (16 men and 16 women; age range, 51 through 92 years, with a mean of 76 years). Nine thromboembolectomy procedures were performed for occlusion less than 1 month in duration (acute), and 23 procedures were performed for occlusion greater than 1 month in duration (chronic). Ten patients (nine with chronic and one with acute occlusion) had thrombectomy of an above-the-knee femoropopliteal graft, and eight patients (six with chronic and two with acute occlusion) had thrombectomy of an infrageniculate femoropopliteal or femorotibial bypass graft. Seven patients had a thrombosed forearm dialysis access fistula (two with chronic and five with acute occlusion). Six patients had obstructions in the distal or proximal native artery. (Angioscopy was used to locate these obstructions.) Blood vessel patency and clinical symptoms were recorded after each procedure. Long-term follow-up data were available for all patients for 1 to 25 months, with a mean follow-up of 7 months.

RESULTS

High-resolution angioscopic images were obtained in all patients, with excellent visualization of the lumen. These images identified the location and nature of the obstruction. A summary of results is presented in the Table. Angioscopy revealed debris or thrombus in all 18 patients who had thrombectomy of a femoropopliteal graft. In four of 10 patients with above-the-knee grafts, neointimal hyperplasia at the distal anastomosis caused graft occlusion and was repaired. In five patients a second bypass graft was placed. In only one case was thrombectomy found to be sufficient. In these nine patients with above-the-knee thromboembolectomy of graft, angioscopy defined the extent of luminal compromise and the obliteration of the lumen in the artery immediately distal to the anastomosis. Of the four grafts that underwent revision, two were widely patent and one was stenotic, and one patient required placement of a new graft for progressive ischemia. Of the five new grafts placed, four remained open without subsequent surgery; however, one patient developed claudication at two blocks. The fifth patient's graft was occluded 7 months after his suprageniculate femoropopliteal bypass graft was converted to an infrageniculate femoropopliteal bypass graft. This patient had claudication at one block and declined further surgical intervention.

Of the eight below-the-knee procedures, two were performed for extraction of emboli and six were performed for late obstruction of bypass grafts. Angioscopy located the emboli and thrombus in those patients with distal bypass grafts and assisted with extraction of the clot with the Fogarty catheter. Balloon inflation in these small arteries could be controlled by direct visualization with the angioscope.

In one patient, distal ischemia 48 hours after infrageniculate femoropopliteal bypass was determined angioscopically to be secondary to an embolus. The embolus was extracted, and blood flow was restored to the lower leg (Fig 1). In six patients, angioscopy suggested that continued attempts at thrombectomy would not result in an acceptable lumen due to intimal flaps or sclerotic vein graft segments. In five of these six patients, graft replacement was initiated on the basis of angioscopic findings. Angioscopic inspection in one patient revealed a distal outflow obstruction of approximately 50%. Intraoperative angiography showed minimal stenosis and the graft was left in place. This graft was occluded within 1 week. A new graft was placed after angioscopic inspection suggested that the outflow obstruction was more significant than previously appreciated. Three patients with in situ grafts had uncut valve leaflets visualized after thrombectomy. The potential for these nondisrupted valves to serve as a nidus for graft obstruction is illustrated in Fig 2. Vigorous attempts at thrombectomy in this case led to disruption of the intimal surface. Although the proximal graft was widely patent, the infragenicular portion of the graft could not be salvaged. Despite graft revision and subsequent new graft placement, this patient's distal circulation was occluded, and below-the-knee amputation was required 8 months after the initial revision. Of the remaining seven patients, five had patent grafts and were without symptoms. One patient had a mild increase in claudication and one patient required placement of a new graft.

Thus, among eight patients, angioscopically guided thromboembolectomy produced seven viable limbs and one below-the-knee amputation. In this series of 18 femoropopliteal thromboembolectomies, new grafts were placed in 10 (56%) of 18 patients and graft revision was performed in seven (39%) of 18 patients. Of these 18 patients, 15 (83%) had significant improvements in their conditions, two (11%) had a return of ischemic symptoms, and one (6%) required an amputation. The overall patency rate, including secondary procedures, was 94% after a mean follow-up of 7 months (range, 1 to 25 months).

In six of seven aortobifemoral grafts, neointimal hyperplasia was identified as the major cause of obstruction. In one case, acute thrombosis from a kink in the graft was identified. Efforts to mobilize and straighten the graft were unsuccessful, and the graft was replaced. In two cases the Fogarty catheter could not extract adherent neointima. Angioscopy permitted the use of a bronchoscopic biopsy brush to extract the adherent neointima. The stages of brush extraction of neointima or adherent thrombus are shown in Fig 3.

Graft patency was maintained in five of these seven patients with aortobifemoral grafts. Of these five patients, three required an additional femoropopliteal bypass for relief of ischemic symptoms. All five grafts in this group remained patent. In one patient, graft occlusion at 15 months necessitated replacement of the entire graft. A second patient, who had reocclusion of the limb of his graft 3 months after thrombectomy, was treated with a femorofemoral bypass graft.

Seven patients had a thrombectomy performed for occlu-

Classification of Angioscopically Guided Thromboembolectomy Procedures

Thrombectomy Location	No. (%)	Acute*	Chronic†	Repeated Thrombectomies	New Grafts	Revised Grafts
Above the knee	10 (31)	1	9	10	5	4
Below the knee	8 (25)	2	6	8	5	2
Arteriovenous fistula	7 (22)	5	2	7	...	...
Aortofemoral	7 (22)	1	6	7	1	6
Total, No. (%)	**32 (100)**	**9 (28)**	**23 (72)**	**32 (100)**	**11 (34)**	**12 (38)**

*Less than 1 month after the initial operation.
†More than 1 month after the initial operation.

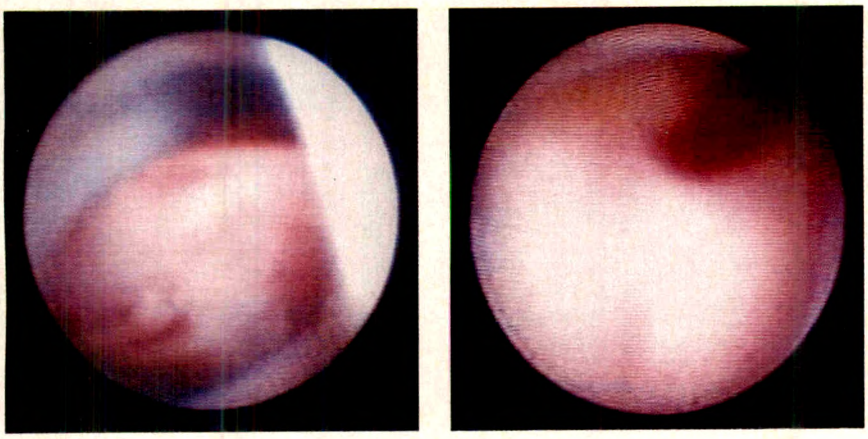

Fig 1.—Left, Angioscopic image of a 48-hour-old embolus in the infrageniculate popliteal graft of a 67-year-old man. The angioscope was passed down the femoropopliteal graft to reveal this subtotal obstruction. Right, After embolectomy, angioscopy revealed a widely patent graft free of debris. This image and vigorous blood flow suggested that completion angiography was not necessary.

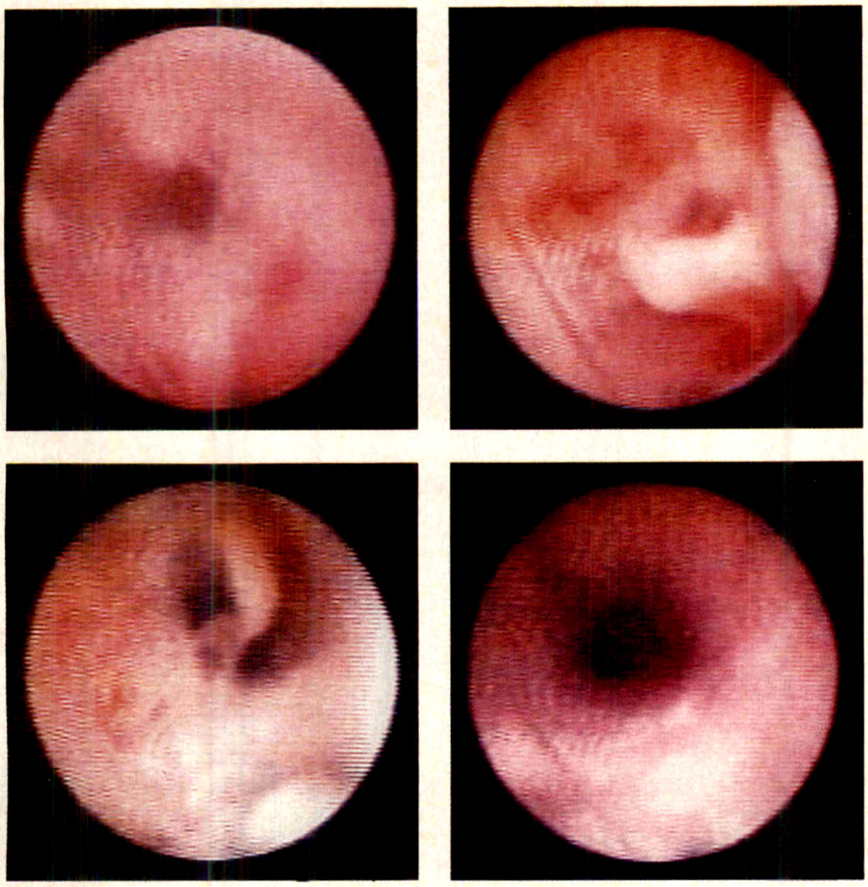

Fig 2.—Top left, Angioscopic image of an in situ saphenous vein bypass graft to the common peroneal trunk of an 87-year-old man with progressive lower-limb ischemia. The lumen is subtotally occluded by thrombus incorporated into an undisrupted valve leaflet extending from the 3-o'clock to the 9-o'clock position. Top right, Distal angioscopic inspection reveals a second area of high-grade stenosis with a prominent flap. Bottom left, In the distal portion of the vein graft, this post-thrombectomy angioscopic image demonstrates a large, long flap that caused luminal obstruction during irrigation. This angioscopic finding necessitated replacement of the distal graft. Bottom right, This angioscopic image shows the above-the-knee portion of the vein graft during final inspection. The lumen is free of thrombotic debris.

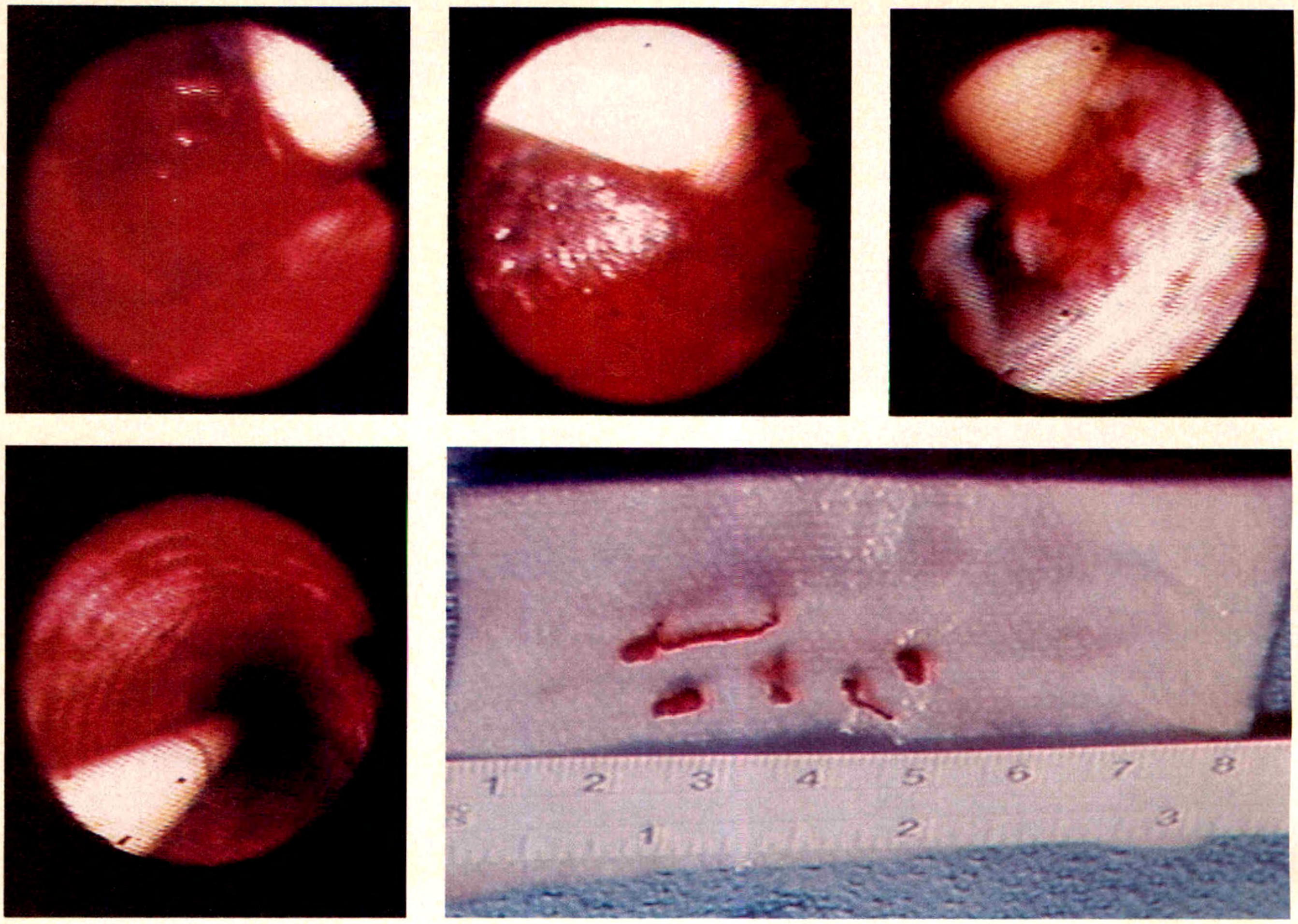

Fig 3.—A, Angioscopic image obtained prior to thrombectomy in an occluded limb of an aortobifemoral graft in a 75-year-old man, showing massive obstruction of the lumen by neointima and thrombus. B, After standard thrombectomy, tenacious neointima was removed with a pulmonary biopsy brush. The brush is seen at the 9-o'clock position. A Fogarty balloon catheter is used to occlude blood flow in the graft at the aortic bifurcation. C, During thrombectomy, debris clings to the walls of the Dacron graft. Continued intraluminal brush manipulation under angioscopic control permits extraction of retained debris. D, Final inspection shows the graft lumen to be free of debris. The occlusive balloon catheter is seen at the 7-o'clock position, extending the length of the graft. E, Thrombotic debris after extraction with the pulmonary biopsy brush. The debris is a mixture of fresh thrombus, neointima, and organized clot.

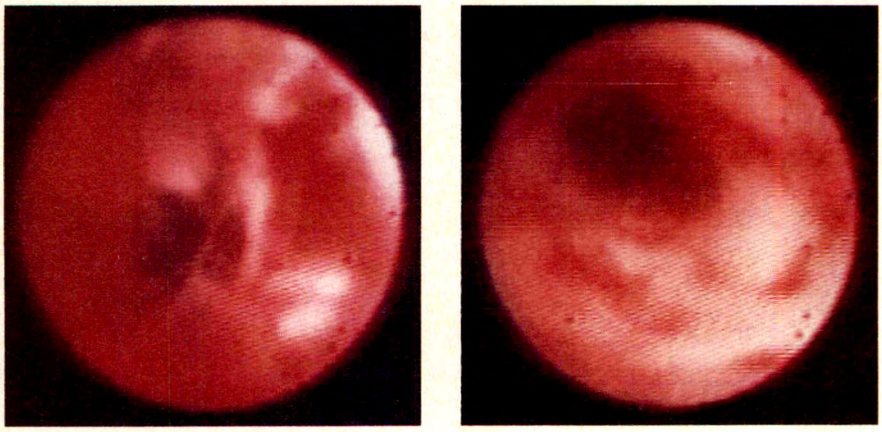

Fig 4.—Left, Prethrombectomy angioscopic image obtained in a dialysis access fistula of the left arm. Thrombus and neointimal flaps fill the lumen. Right, After thrombectomy, angioscopy revealed a wide-open lumen with only scattered patches of thrombotic debris. No further extractions were performed.

sion of an arteriovenous dialysis access fistula. In each case (after routine thrombectomy) angioscopy showed a significant amount of retained thrombus (Fig 4). Angioscopy permitted extraction of the retained thrombus without the need for graft revision. However, subsequent procedures, including three repeated thrombectomies and one balloon angioplasty of an arterial anastomosis, were required. In two patients, profound hypotension appeared to be the cause of subsequent thrombosis. In one patient, a stenotic arterial anastomosis was dilated by balloon angioplasty and remained open. Our overall short-term results are summarized in the Table. In this series, angioscopic information in 32 patients led to thrombectomy in all patients, graft revisions in 12 patients, and placement of new grafts in 11 patients.

COMMENT

Our results suggest that angioscopy permits the surgeon to assess the completeness of balloon thrombectomy, particularly when completion angiography is difficult. In cases with dialysis access fistulas and occluded segments of aortofemoral bypass graft, angioscopy clearly identifies the need for further debris extraction, despite negative results of catheter embolectomy. In vein grafts, angioscopy is very effective at distinguishing thrombus from intimal flaps and retained valves. Although our series is small, our data suggest that angioscopy provides improved technical results compared with thrombectomy.

Angioscopy does not replace preoperative angiography. We continue to believe that preoperative angiography is beneficial in providing the location and extent of stenosis and occlusion. However, once the thrombectomy has begun, angiography cannot determine the nature of the occlusion or the extent of changes made without a repeated angiogram. Furthermore, it is relatively inconvenient to perform multiple angiographic procedures as the thrombectomy proceeds. In contrast, angioscopy can be performed concurrent with the thrombectomy, providing detailed information on the location and extent of residual debris. Since angioscopy facilitates the procedure and decreases dye load, we believe angioscopy should be performed during thrombectomy if the surgeon is familiar with the technique and the technology is available.

All surgeons performing angioscopies in this series had extensive experience. In addition, a second trained observer was present in the operating room to confirm angioscopic observations. In light of the potential to overread the findings of angioscopy, our group was careful not to repeat thrombectomy, revise grafts, or replace grafts unless significant thrombus, obstruction, or graft damage was observed. However, we repeated thrombectomy whenever angioscopic inspection revealed significant luminal compromise due to thrombus.

Completion angiography at the time of angioscopy was performed in only eight cases; thus, direct comparison of the two modalities is not feasible in this study. However, in 16 patients the surgeon decided not to perform completion angiography based on angioscopic information. This was particularly helpful in patients with renal failure or high creatinine levels or in patients who had already received significant dye loads. Of eight patients who underwent completion angiography followed by angioscopic inspection, arteriography significantly underestimated or missed the presence of retained thrombus and debris. In two cases, significant stenosis of the distal anastomosis was found on angioscopy but not on angiography.

Our experience is consistent with that of White et al,[8] Vollmar and Hutschenreiter,[9] and Miller et al.[6] In each series, angioscopy identified significant residual thrombus, even when retrograde blood flow was observed. Miller et al noted that angiography significantly underestimated the volume of residual thrombus, and White et al noted a significant disparity between angioscopy and angiography. We view angioscopy as complementary to angiography. Angiography provides an overall road map in defining the arterial tree, while angioscopy permits direct observation of specific portions of the arterial anatomy.

Angioscopy is more sensitive than angiography to the presence of thrombus and luminal obstruction.[5] Our studies suggest that careful attention to detail is necessary for proper interpretation of angioscopic results. Because angioscopy presents the vascular surgeon with a highly magnified view, small strands of residual thrombus may appear to be larger than they really are. It is therefore important to use the shaft of the Fogarty catheter for size comparison. This prevents overly aggressive attempts to remove every last strand of thrombus. Repeated attempts at debris extraction, particularly in native arterial segments or vein grafts, may turn success into failure. In addition, angioscopic findings may prompt placement of a new graft, as in 10 cases of infrainguinal bypasses in the present series.

Previous studies of arterial thromboembolism demonstrated that secondary procedures can achieve a high rate of good long-term functional success.[10-13] In the present limited series, graft patency was maintained in 94% of patients through a combination of graft revision and graft replacement. Repeated bypass procedures were performed in seven (28%) of these 25 patients with aortobifemoral or infrainguinal grafts. Follow-up in the group ranged from 1 to 25 months.

Our experience suggests that the high rate of repeated procedures required after thromboembolectomy may be due to unrecognized injury caused by the balloon catheter itself.[14] Since angioscopy can show the extent of balloon inflation, it may help minimize traumatic damage to the arterial wall. When damage is already present due to thrombosis or atherosclerosis, angioscopy may be more effective than angiography in determining which grafts need revision or replacement. We believe angioscopy provided an improved technical result, as completion angiography was less sensitive to retained thrombus and luminal obstruction. In many cases a normal completion angioscopic view will obviate the need for concomitant angiography.

This study was supported in part by Imperial Grand Sweepstakes and Grand Sweepstakes of Cedars-Sinai Medical Center and also by grant HL-17651 from the Specialized Centers of Research in Ischemic Heart Disease of the National Heart, Lung, and Blood Institute. Dr Grundfest is a recipient of clinical investigator award 1K087 HL-01522 from the National Heart, Lung, and Blood Institute.

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Discussion

S. ERIC WILSON, MD, Torrance, Calif: Novelty is not enough. Before we accept a new device, it should meet at least four criteria. First, it should consistently perform better than existing techniques, in this case, the completion angiogram. The direct view afforded by the angioscope literally adds a new dimension to the black-and-white negative images of the arteriogram. Second, it must be practical, so that on short notice in emergencies and in the evening hours, instrumentation would be readily available to the surgeon without the assistance of a biomedical engineer to set up the equipment. The modular "ready-to-plug-in" video setup and disposable angioscopes have made this practical. Third, it must be safe. The only complication other than those related to blood vessel cannulation appears to be the slight risk of volume overload in the elderly patient. Last, it must be cost-effective. How much does the use of the angioscope add to the cost of the procedure?

We recently presented (White GH, White RA, Kopchok GE, et al. *J Vasc Surg.* 1990;11:280-288) our experience with endoscopically directed thromboembolectomy in 73 patients. In the majority of these patients, retained thrombus was observed after no more clot could be obtained with the Fogarty catheter. In two thirds of these patients, this allowed us to repeat the balloon embolectomy, now guided with the angioscope. In some patients, biopsy forceps were useful in extracting plaques, and in others adherent clot was removed with a brush. The angioscope was helpful in directing us to additional operation or angioplasty. The angioscope is particularly useful in guiding the Fogarty catheter into the branches of the popliteal artery large enough to accept both the angioscope and the embolectomy catheter. After thrombectomy of a clotted graft, the angioscope may disclose intimal hyperplasia at the distal anastomosis, allowing the surgeon to devise a method of local revision or use a short jump graft to a more distal, favorable runoff vessel. In some cases we have found that a distal incision alone may be sufficient to perform the thrombectomy and also to revise the distal anastomosis.

The angioscope is also very useful in thromboembolectomy of native blood vessels. An embolus can be distinguished from thrombus forming in an already atherosclerotic artery. Extraction of the clot alone under these circumstances, even with anticoagulation, is often followed by rethrombosis, since the cause has not been corrected. In these patients I believe the best procedure is an early femoropopliteal bypass. Inspection of the interior of the artery with the angioscope may aid in making that important decision.

To what extent have you and your coworkers incorporated angioscopy into your daily practice? Have you replaced completion arteriography with angioscopic examination? Do you recommend routine use of the angioscope at each vascular procedure? Do you think our ability to get a more complete thrombectomy with the angioscope will generate new enthusiasm for venous thrombectomy? Have you infused thrombolytic agents through the channel in the angioscope? How useful are the very small 0.4- to 0.8-mm angioscopes that do not have an irrigation channel?

ERIC W. FONKALSRUD, MD, Los Angeles, Calif: Can one apply the technique to small blood vessels? What is the size limit of the technology?

EUGENE BERNSTEIN, MD, La Jolla, Calif: The angioscope is opening a new form of vascular surgery: a surgeon-performed endovascular procedure guided by the angioscope, using the tools interventional radiologists use, such as balloons, Simpson cutters, and other atherectomy devices. I believe we are now ready to adapt the tools of the arthroscopist and the dentist to this kind of work. What kinds of instruments have the authors used with the angioscope?

JOHN R. BENFIELD, MD, Sacramento, Calif: Has the angiographer started to use angioscopes as an adjunct? If not, when do you project this?

DR TREIMAN: At present neither the surgeon nor the hospital charges the patient for the procedure. I suspect that in the very near future the hospital will charge the patient, but the surgeon will not. Angioscopy has become a very important part of our practice. We have a fellow who is in charge of the equipment, assists with the procedure, and ensures that the instrumentation is functional. I suggest that, if you go into this field, you should employ such a dedicated person to ensure that the angioscopes are cleaned properly, cared for, and available when needed. It is very disheartening to see an $8000 angioscope broken by someone who is not familiar with the equipment. In general, we have not replaced completion angiography with angioscopy. In selected cases we rely on the angioscopic findings and have not done completion angiography, ie, in the patient with a high creatinine concentration or renal failure. We have not used the angioscope for venous thrombectomy, primarily because we do not perform venous thrombectomy. It is an intriguing idea. To my recollection, we have not used the angioscope in conjunction with thrombolytic therapy. We have used very small angioscopes percutaneously in conjunction with coronary work. We have done peripheral vascular angioscopy percutaneously. Dr Bernstein, we have used angioscopes with lasers and with percutaneous transluminal angioplasty as well. Percutaneous coronary angioscopy is being investigated, although the authors, with the exception of Drs Grundfest and Segalowitz, have not been involved in that work.

Massive Splenomegaly

Superior Results With a Combined Endovascular and Operative Approach

Jonathan R. Hiatt, MD; Antoinette S. Gomes, MD; Herbert I. Machleder, MD

• Splenectomy for massive splenomegaly (drained splenic weight, >1000 g) has an uncommonly high morbidity and mortality because of technical challenges and problems of hemostasis. In a group of 10 patients with massive splenomegaly due to myeloproliferative disorders (average splenic weight, 4193 g), we developed a management algorithm based on preoperative angiographic embolization of the splenic artery. Average operating time was 1.7 hours (range, 1 to 2.5 hours). Average blood loss was 528 mL; six of the 10 patients had blood loss less than 250 mL. There were four minor complications and one major complication (gastric ulcer requiring reoperation). There were no deaths in the perioperative period, and no patients required reoperation for hemorrhage.

(*Arch Surg.* 1990;125:1363-1367)

Of the various indications for splenectomy, massive splenomegaly has the greatest morbidity and mortality. Technical problems may be formidable and often are compounded by the underlying disease processes causing splenomegaly. Pancytopenia and immune compromise are common consequences both of the diseases and of their treatment.

Operative hemostasis represents the greatest technical obstacle, for a number of reasons. First, the spleens may reach huge proportions, with consequent hypervascularity. Previous operations in the upper part of the abdomen and use of irradiation to control the infiltrative process causing splenomegaly compound these difficulties by producing extensive adhesions between the splenic capsule, diaphragm, and parietes. Second, thrombocytopenia caused by hypersplenism and medications aggravates the operative bleeding. Finally, these cases are relatively infrequent, even in centers with a busy hematology service, and the experience of the individual surgeon is therefore limited.

During operation, early ligation of the splenic artery has been advocated as a useful maneuver to decrease blood loss. Endovascular radiologic techniques now permit angiographic occlusion of the blood supply to various organs, including the spleen. Splenic artery embolization without operation has been used to treat the hematologic effects of hypersplenism but does not relieve local symptoms associated with the huge spleen itself and often leads to increased local pain and systemic toxic manifestations of the splenic infarction and necrosis. In 1975, Smith et al[1] reported the use of preoperative embolization to enable resection of a large hemangiopericytoma in a patient who remains alive and well. In 1980, Hocking et al[2] reported on our group's first experience with angiographic embolization of the splenic artery before splenectomy in a patient with polycythemia rubra vera and splenomegaly. Subsequent use of this approach led to the development of a treatment algorithm that forms the basis of this report.

PATIENTS AND METHODS

Patients

Patients referred to us for splenectomy because of massive splenomegaly (defined by drained splenic weight >1000 g) were treated with a protocol of preoperative angiographic embolization. Ten patients were seen, one in 1978 (described previously[2]) and nine in the past 7 years. Seven were male and three were female, with an average age of 45.8 years (range, 21 to 71 years). Hematologic diseases included chronic myelogenous leukemia in seven patients, myelofibrosis in two, and polycythemia rubra vera in one. Nine patients were receiving antileukemic chemotherapy, including hydroxyurea (seven patients), hydroxyurea plus busulfan (one), and prednisone (one).

All patients had a large, palpable abdominal mass. The principal indications for splenectomy included splenic size, with chronic pain and inability to eat (five patients); rapid, acute splenic enlargement (two patients); and before bone marrow transplantation, with the goals of removal of residual leukemic cells and correction of the hematologic disorders of hypersplenism (three patients). Eight patients were anemic (hematocrit, <0.30). White blood cell count was normal in one patient, elevated ($>10.0 \times 10^9$/L) in eight, and depressed ($<4.0 \times 10^9$/L) in one. Platelet count was normal in two patients, elevated ($>450 \times 10^9$/L) in two, and depressed ($<100 \times 10^9$/L) in six.

One patient was treated emergently because of rapid splenic enlargement, with angiographic embolization and operation accomplished within 3 hours of surgical consultation. Operation was semielective in the remaining nine patients. Angiography and embolization were performed 1 day before operation in seven patients and on the day of surgery in two.

Management Protocol

In most instances, angiography was scheduled for the afternoon and operation the following morning. Patients were given nothing by mouth, an intravenous line was started, and blood was drawn for determination of complete blood cell count, platelet count, coagula-

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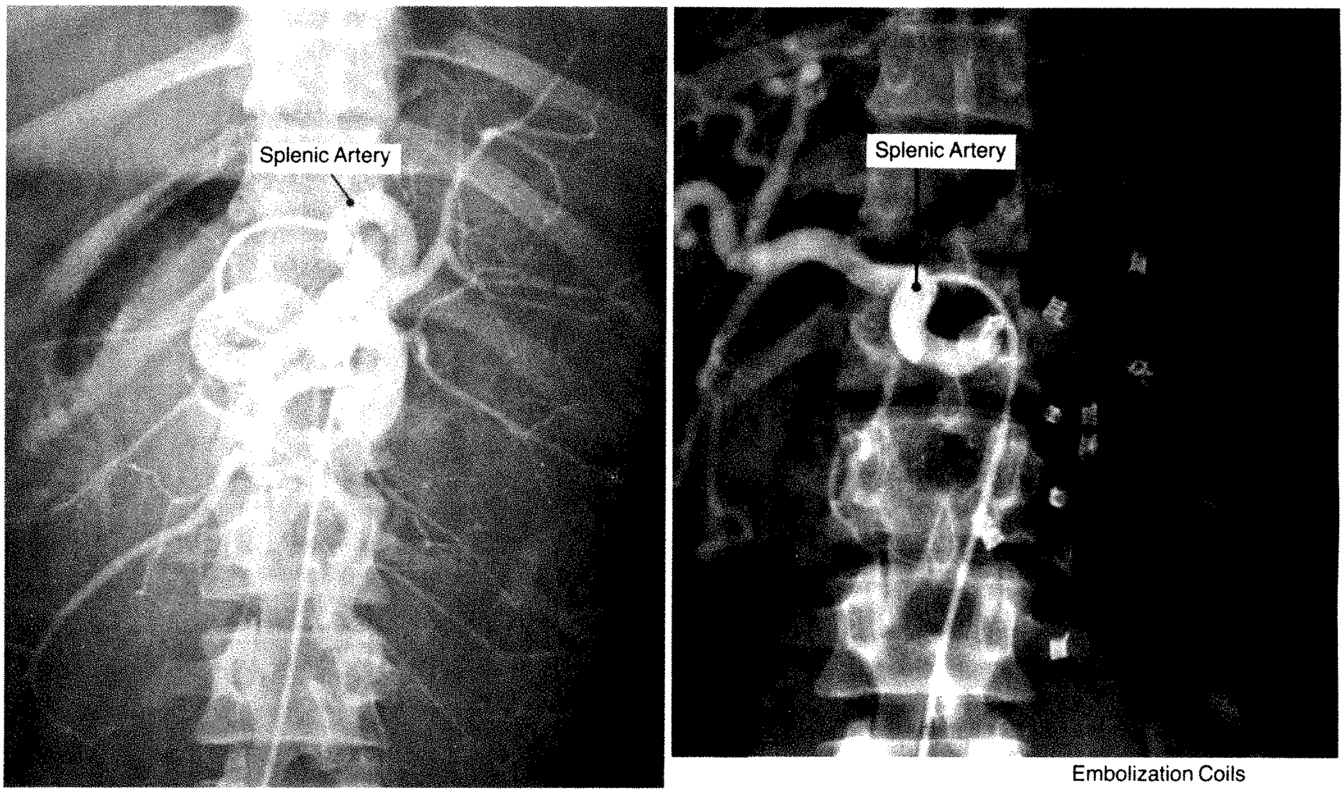

Fig 1.—Left, Celiac artery injection shows a tortuous, elongated splenic artery supplying a markedly enlarged spleen. Right, Postembolization arteriogram shows the splenic artery occluded a few centimeters beyond its origin with Gianturco-Wallace coils and gelatin sponge. With splenic artery occlusion, there is now filling of the hepatic artery on the celiac artery injection.

tion measures, and crossmatch, with additional studies as needed for individual patients. Except for the patient requiring emergency splenectomy, all patients received pneumococcal vaccine (Pneumovax; Merck Sharp & Dohme, West Point, Pa) 1 to 2 weeks before operation.

Angiography.—The splenic artery was catheterized from a femoral approach with the use of a 5- or 6.5-F preformed catheter. A preliminary splenic or celiac arteriogram was obtained to visualize the size and course of the splenic artery and the location of its major branches (Figs 1, left, and 2, left). Subsequently, the catheter was advanced to the middle or distal portion of the splenic artery, and transcatheter embolization was performed. In nine patients, embolization was accomplished by means of Gianturco-Wallace coils with interposed pledgets of gelatin sponge (Gelfoam; The Upjohn Co, Kalamazoo, Mich) (Fig 1, right). In one patient, a small amount of collagen (Avitene; Alcon Laboratories Inc, Fort Worth, Tex) was administered in addition to the coils and gelatin sponge. Detachable latex balloons were used alone for embolization in another patient (Fig 2, right). The embolization procedure was terminated when there was no forward flow in the splenic artery. Embolization was confined to the main splenic artery, and no attempt was made to occlude the intrasplenic branches. If the catheter could not be advanced to a point distal to the takeoff of the pancreatic branches, care was taken during placement of the gelatin sponge pledgets to avoid particulate embolization of these vessels.

Strict aseptic technique was used during the radiologic procedure. All patients were treated with systemic antibiotics administered immediately before the procedure and continuing into the postoperative period. Eight patients received cefazolin sodium alone, one patient received vancomycin hydrochloride, and one received piperacillin sodium and ceftazidime. In two patients, the gelatin sponge particles were suspended in a cefazolin sodium solution (1 g in 50 mL of saline). In two patients, bupivacaine hydrochloride (5 mL) was injected intra-arterially into the splenic artery during the embolization procedure to decrease postembolization pain. Abdominal pain and tenderness over the spleen were the rule after splenic embolization and were treated with parenteral analgesics. Low-grade fever also was a common response.

Operative Approach.—All procedures were performed by a surgical resident and one of us (J.R.H. or H.I.M.). A midline incision was used in five patients, and a left subcostal incision with extension into the right rectus sheath was used in five (Fig 3, left). The spleen was mobilized by dividing the posterior attachments, then lifted from the abdomen by the assistant so that the vessels could be controlled in continuity with individual ligatures and transfixion sutures (Fig 3, right). Splenic artery ligation proximal to the hilum of the spleen was neither needed nor attempted in any patient. A Silastic Jackson-Pratt drain was used in one patient and removed several days after operation.

RESULTS

Average anesthesia time was 2.5 hours (range, 1.7 to 3.5 hours), and average operating time was 1.7 hours (range, 1 to 2.5 hours). Average blood loss was 528 mL (range, 75 to 2500 mL). Blood loss was less than 250 mL in seven patients. Two patients with previous upper abdominal operations had blood loss of 500 and 1200 mL, and one patient with myelofibrosis who had received nine courses of splenic irradiation had blood loss of 2500 mL.

Average size of the resected spleen was 5802 cm^3 (range, 2442 to 10 290 cm^3), and its average weight was 4193 g (range, 1400 to 6275 g). Results of histologic examination were compatible with the underlying hematologic process, showing various degrees of parenchymal infiltration by abnormal cells, stromal fibrosis, and extramedullary hematopoiesis. Infarction was not a feature, with parenchymal necrosis being seen in only one spleen.

Overall blood transfusion requirement was 3.7 U (range, 0 to 7 U) for the 10 patients. One patient required no transfusions, and one required preoperative blood transfusion only.

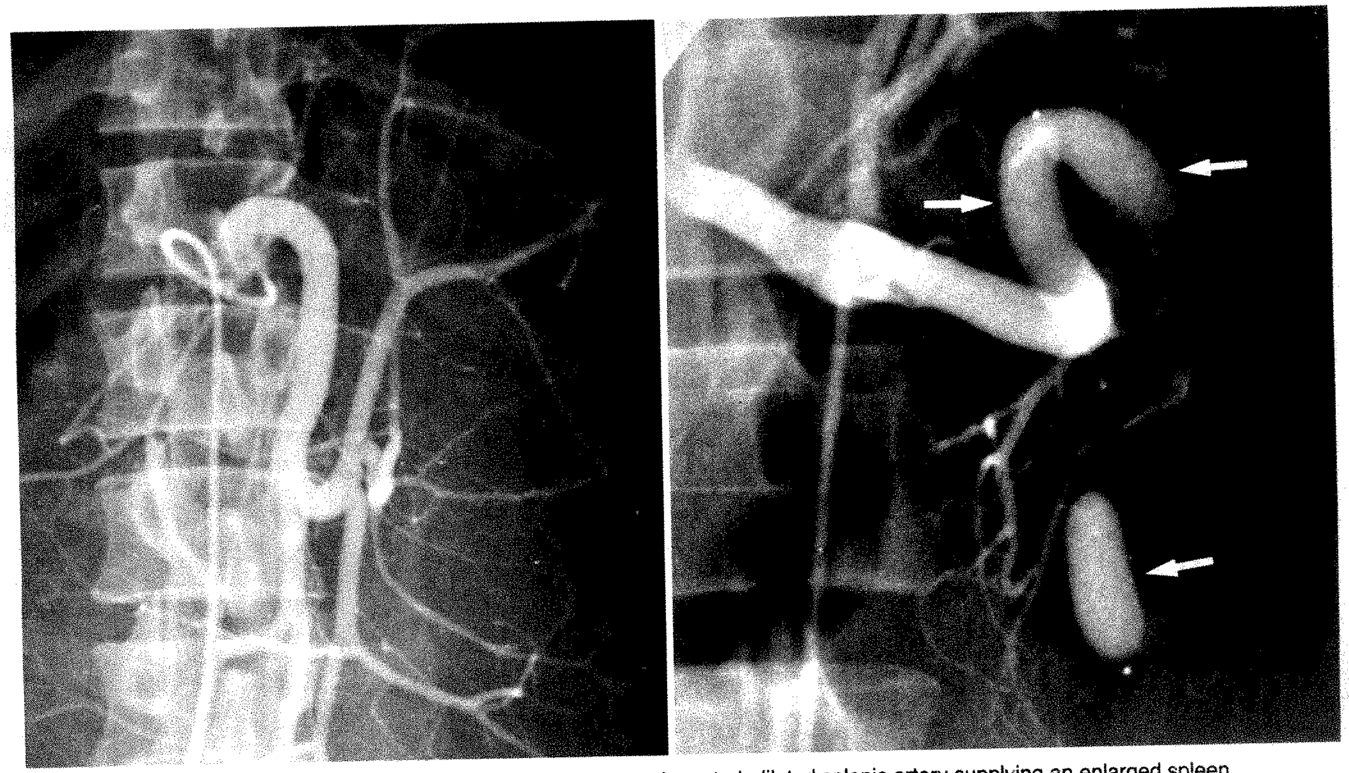

Fig 2.—Left, Selective splenic artery injection shows an elongated, dilated splenic artery supplying an enlarged spleen. Right, Postembolization arteriogram shows occlusion of the splenic artery with detachable latex balloons (arrows).

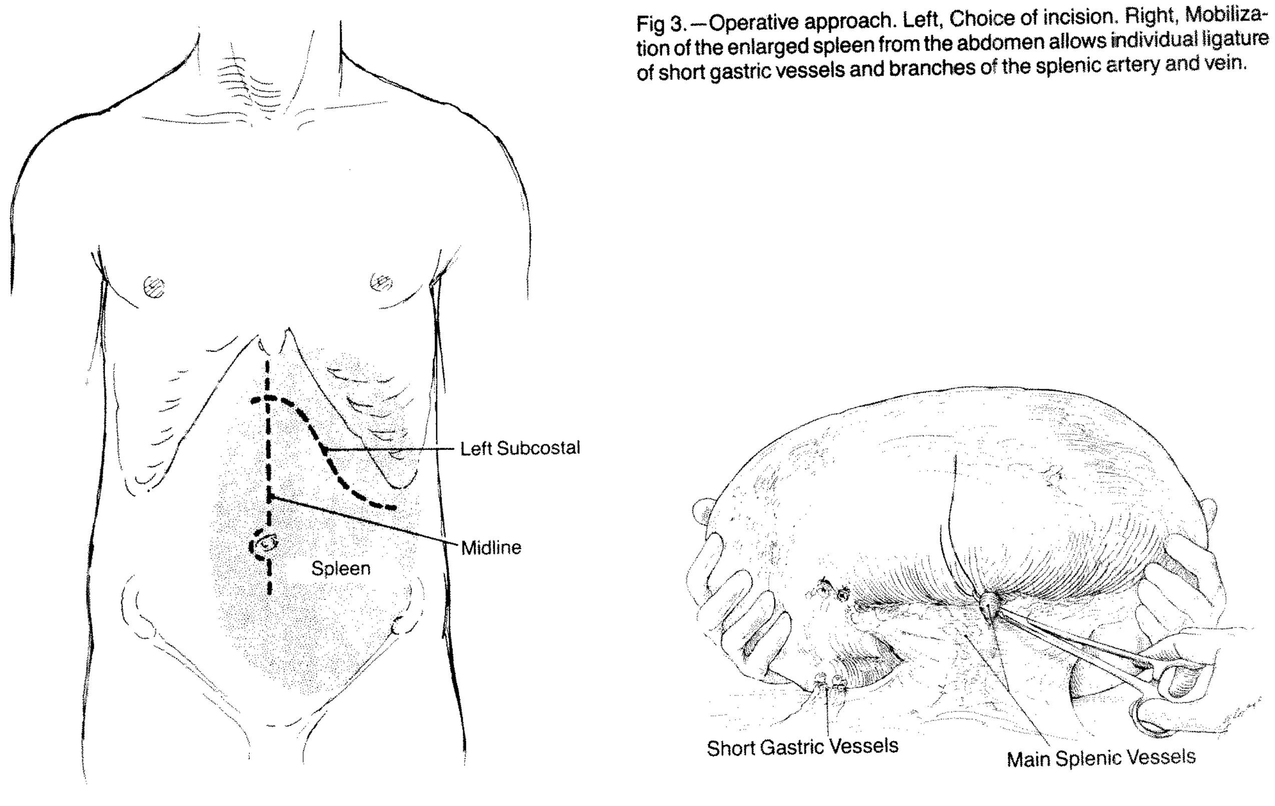

Fig 3.—Operative approach. Left, Choice of incision. Right, Mobilization of the enlarged spleen from the abdomen allows individual ligature of short gastric vessels and branches of the splenic artery and vein.

Splenectomy for Massive Splenomegaly

Source	n	Average EBL, mL*	Major Complications, %	Postoperative Abdominal Hemorrhage, %	30-d Mortality, %
Morgenstern[15]	16	ND	19	13	13
Goldstone[16]	34	ND	56	26	15
Wobbes et al[17]	49	ND	43	10	2
Bickerstaff and Morris[18]	47	ND	30	2	0
Johnson and Deterling[19]	36	6241†	31	6	11
Coon[20]	51	>1000	20	4	8
Present series	10	528	20	0	0

*EBL indicates estimated blood loss; ND, not determined.
†In patients with complications.

The remaining eight patients received intraoperative and/or postoperative transfusions of blood (average, 3.75 U), and four of them received transfusions of platelets (average, 14 U).

There were no deaths in the perioperative period. Five patients had complications, three as a result of the operation and two as a result of the angiography. Angiographic complications included a small groin hematoma that resolved spontaneously in one patient and embolization of the tail of the pancreas in the patient who received an injection of collagen in addition to coils and gelatin sponge. At operation, the pancreatic tail appeared dusky and was surrounded by a small zone of fat necrosis. The patient developed mild hyperamylasemia (twice the normal serum amylase level), which resolved without sequelae. Pneumonitis was a minor postoperative complication in two patients. The single major complication was a bleeding gastric ulcer 2 weeks after splenectomy and 1 week after discharge, which required reoperation for control. The ulcer was located on the proximal greater curvature on the luminal side of a suture-ligated short gastric vessel.

Average hospital stay was 12.3 days (range, 8 to 24 days). Average postoperative stay was 9.4 days (range, 5 to 21 days). Three patients died within 3 months of operation with accelerated progression of their hematologic malignant neoplasms. Two patients who received successful bone marrow transplants after splenectomy and the remaining five patients were in stable condition at 6 months to 1 year of follow-up.

COMMENT

Transcatheter embolization is an effective technique to produce occlusion of the splenic artery and has been used in the treatment of various pathologic processes, including splenic artery aneurysms[3] and hypersplenism due to portal hypertension or blood dyscrasias. Complete splenic embolization for treatment of hypersplenism was first described by Maddison.[4] Subsequent reports of total ablation of splenic blood flow by embolization techniques described a high morbidity due to splenic abscess, pancreatitis, pneumonia, and septicemia.[5-10] Grave complications, such as splenic rupture,[8] limited the application of total embolization therapy. Spigos et al[11] and Owman et al[12] demonstrated that the complication rates could be reduced significantly when partial embolization was performed and accompanied by use of prophylactic antibiotics and meticulous pre-embolization and postembolization care. Current recommendations for embolization therapy in the treatment of hypersplenism call for partial arterial occlusion, stopping when roughly two thirds of the spleen is ablated.[11] Partial embolization allows persistence of a portion of viable spleen and preservation of some splenic function.

A variety of agents have been used to occlude the splenic artery. Coils and balloons cause occlusion of the main trunk of the vessel. Changes in the splenic parenchyma are minimal, since distal collateral circulation is usually maintained. If it is the intent to leave the spleen in place after embolization and parenchymal ablation is desired, the splenic artery may be occluded proximally, distally, or at the level of the hilum. Intrasplenic branch occlusion also produces ablation but has been found to be associated with longer persistence of minor complications.[13] It is best to avoid embolization of the pancreatic arterial branches with small particulate agents, such as gelatin sponge or polyvinyl alcohol sponge granules that reach the capillary level (Ivalon; Unipoint Industries, High Point, NC), as this may produce pancreatic necrosis. Embolization of the distal branches of the short gastric arteries is tolerated well as long as the collateral circulation has not been compromised by previous gastric operation.[14]

Morgenstern[15] described the fundamental principles of operative therapy and perioperative treatment of patients requiring splenectomy for myeloid metaplasia in an era preceding development of endovascular radiologic techniques. Review of reported experiences[15-20] (Table) shows that the morbidity and mortality are substantial. The usual indications for splenectomy are splenic size and cytopenias, and because most of the diseases are characterized by short survival, the operations are appropriately regarded as palliative. Technical problems, particularly postoperative hemorrhage, and operative mortality are features of virtually every series.

Control of bleeding is the greatest technical challenge, and the traditional approach has been to ligate the splenic artery in the lesser sac before mobilizing the spleen. Without arterial occlusion, the massive spleen bleeds severely even from capsular tears that would be relatively innocuous in patients with smaller spleens and normal hematologic values. However, splenic artery ligation is often a difficult maneuver in these patients, hindered by typical engorgement of the artery and by bleeding from the peripancreatic tissues. Recognizing these limitations of conventional therapy, we have developed a management protocol based on preoperative angiographic embolization of the splenic artery.

Using this protocol, we report herein the treatment of 10 patients with massive splenomegaly demonstrating low transfusion requirements, short operation times, no reoperations for bleeding, and no operative mortality. Technical facility of the operation after angiographic embolization has been particularly striking, converting the procedure from a stressful challenge for senior surgeons to a pleasant teaching experience that may be shared with a surgical resident. The overall complication rate remains significant, in part a function of the underlying diseases and in part a reflection that this is a major operative procedure.

Several aspects of this approach deserve emphasis. A management team is needed, including the hematologist, the surgeon, and an experienced interventional radiologist. At angiography, the splenic artery may be occluded at any point, but care should be taken to avoid embolization of pancreatic vessels with small particles. Prophylactic antibiotics should be used, and adequate analgesia after the embolization procedure is important to minimize splinting and pulmonary complications. Finally, the operation should be performed soon after embolization, at most 24 hours, to minimize discomfort to the patient and the risk of infection of the ischemic spleen.

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Discussion

LEON MORGENSTERN, MD, Los Angeles, Calif: The authors' approach has been useful and successful in their hands. Nevertheless, I disagree and definitely recommend against routine splenic artery embolization before removal of the massively enlarged spleen. In my own experience with many such spleens with diverse abnormalities, I have rarely found it difficult to do a preliminary ligation of the splenic artery, which accomplishes exactly the same objective with less risk, less apprehension, less pain, less labor, and less cost.

Massive splenic enlargement practically delivers the large serpentine splenic artery to the midoperative field, where, after opening of the lesser sac, it can be safely and easily encircled with a vessel loop or doubly tied. Within 10 minutes, there is a 10% to 15% reduction in splenic volume, which not only facilitates mobilization, but also delivers an immediate autotransfusion. During this period we proceed along the greater curvature with serial double ligation of the gastroepiploic branches and the vasa brevia. I think it is easier to deliver the massive spleen atraumatically than it is to mobilize the small spleen hidden in the recesses of the left upper quadrant. Where, then, are the risks of catastrophic bleeding in the removal of these splenic behemoths? There really should be none.

When does major bleeding occur? It occurs if the fragile main splenic veins are approached anteriorly; if the highest vasa brevia, usually very engorged, are torn during delivery of the upper pole; if bleeding from preventable capsular avulsions are not controlled by topical hemostasis; and if there are dense vascular adhesions to the parietal peritoneum, secondary to infarct, neoplastic infiltration, or radiation. There are maneuvers to deal with each of these exigencies. In my opinion, previous arterial embolization obviates none of these difficulties.

What difficulties does embolization add? These patients frequently have coagulation problems. Why invite another one with the femoral artery at the groin? Why risk ischemic damage to the distal pancreas? Why add the painful experience of splenic infarction or partial infarction, a preoperative prelude that is hardly conducive to a calm preoperative experience. What if there is unforeseen delay in the operative procedure, with the ischemic spleen in situ, subject to all the ills that such "flesh is heir to"? And, finally, why add additional cost and complexity to the procedure, at an estimated level of $1000 to 1500?

Nevertheless, there is a place for selective preoperative embolization—when it can be specifically predicted that splenic artery ligation will be difficult or impossible. Included here are portal hypertension, previous gastric or pancreatic surgery, previous pancreatitis, or known infiltration of the periarterial tissues. In such instances, previous embolization is useful. I, however, would prefer to have it done closer to the operative period, rather than on the day before. My own experience belies the necessity of this approach routinely.

THEODORE X. O'CONNELL, MD, Los Angeles, Calif: In the majority of cases with massive splenomegaly, it is rather an easy operation. The massive spleen is delivered outside the wound with a long vascular radicle. In a small minority of patients who have had previous radiation, operation, etc, there are a lot of vascular adhesions and the spleen is stuck to the diaphragm and is hard to deliver. Therefore, the major difficulty is one of adequate exposure. The authors' average blood loss is acceptable. Between mean or the median vs the range, there is a significant difference. Three patients had severe bleeding, up to 2500 mL; all of these were those who had difficult splenomegalies. It does not appear that splenic artery embolization made a difference in those very patients in whom we want it to make a difference.

MAX R. GASPAR, MD, Long Beach, Calif: To prevent some of the problems with embolization, would it not be better to put a balloon catheter in percutaneously on the morning of the operation to control the splenic artery? I have done that, and it works very well.

DR HIATT: Dr Morgenstern, your technique reflects the highest standard that may be achieved. We have presented a series representative of current practice. After splenic artery embolization, operative bleeding is reduced dramatically compared with that in reported series. Ligation of the large, fragile splenic artery, with a definite risk of injury to the pancreas, is a dangerous maneuver that may be avoided.

Addition of the embolization procedure to the care of very ill and immunosuppressed patients does represent an intervention with its own morbidity and cost. The splenectomy itself is palliative and rarely has long-term influence on the underlying hematologic disease. However, the patients are reaching the surgeon at more advanced stages of disease, often after treatment with radiation and chemotherapy, with ever-greater operative risk. Therefore, any means to reduce operative complications seems to offer a clear-cut advantage. An experienced interventional radiologist is a crucial member of the team. As these techniques become more widespread, costs may decline.

Dr O'Connell, our largest blood loss is lower than the median or mean losses in reported series. With embolization, blood loss is diminished significantly even for the difficult cases with postoperative adhesions or irradiation.

Dr Gaspar, the radiologic procedure can be done on the day of operation, and the occlusion balloons may be used, but we have found that the infarction process decreases the vascularity of the adhesions and allows the platelet count to rise during the night before the operation.

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Zinacef* **(sterile cefuroxime sodium, Glaxo)** **Zinacef*** **(cefuroxime sodium injection)** **BRIEF SUMMARY**

The following is a brief summary only. Before prescribing, see complete prescribing information in Zinacef* product labeling.

INDICATIONS AND USAGE: Zinacef* is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections**, including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp, *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing), *Streptococcus pyogenes*, and *Escherichia coli*.
2. **Urinary Tract Infections** caused by *E coli* and *Klebsiella* spp.
3. **Skin and Skin Structure Infections** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, *E coli*, *Klebsiella* spp, and *Enterobacter* spp.
4. **Septicemia** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pneumoniae*, *E coli*, *H influenzae* (including ampicillin-resistant strains), and *Klebsiella* spp.
5. **Meningitis** caused by *S pneumoniae*, *H influenzae* (including ampicillin-resistant strains), *Neisseria meningitidis*, and *S aureus* (penicillinase- and non-penicillinase-producing).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *S aureus* (including penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Zinacef has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to Zinacef.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Zinacef may be used concomitantly with an aminoglycoside (see PRECAUTIONS). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of Zinacef may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (eg, vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Zinacef should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of Zinacef has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that Zinacef therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS: Zinacef* is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH ZINACEF* IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: Although Zinacef* rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of Zinacef should be reduced in patients with transient or persistent renal insufficiency (see DOSAGE AND ADMINISTRATION), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of Zinacef may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Drug/Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest* tablets), but not with enzyme-based tests for glycosuria (eg, Tes-Tape*). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving Zinacef.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since Zinacef is excreted in human milk, caution should be exercised when Zinacef is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS: Zinacef* is generally well tolerated. The most common adverse effects have been local reactions following intravenous administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with intravenous administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in less than 1% of the patients treated with Zinacef and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in less than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (less than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics.

Adverse Reactions: Toxic epidermal necrolysis, fever, vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Prolonged prothrombin time, pancytopenia, agranulocytosis, thrombocytopenia.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zinacef* product labeling.)

Impaired Renal Function: A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see Table 1 in product package insert).

HOW SUPPLIED: Zinacef* in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected from light. Zinacef is a dry, white to off-white powder supplied in vials and infusion packs as follows:

NDC 0173-0352-31 750-mg* Vial (Tray of 25)
NDC 0173-0354-35 1.5-g* Vial (Tray of 25)
NDC 0173-0353-32 750-mg* Infusion Pack (Tray of 10)
NDC 0173-0356-32 1.5-g* Infusion Pack (Tray of 10)
NDC 0173-0400-00 7.5-g* Pharmacy Bulk Package (Tray of 6)

Zinacef frozen as a premixed solution of cefuroxime sodium should not be stored above -20°C. Zinacef is supplied frozen in 50-ml, single-dose, plastic containers as follows:

NDC 0173-0424-00 750-mg* Plastic Container (Carton of 24)
NDC 0173-0425-00 1.5-g* Plastic Container (Carton of 24)
*Equivalent to cefuroxime.

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The Recalcitrant Perineal Wound After Rectal Extirpation

Applications of Muscle Flap Closure

James P. Anthony, MD, Stephen J. Mathes, MD

• Perineal wounds developing after abdominoperineal resection result in chronic purulent drainage and intermittent episodes of sepsis and are generally unresponsive to conservative medical and surgical treatment. Thirteen consecutive patients (aged 27 to 74 years; mean, 48 years) who underwent débridement and immediate muscle flap closure of these wounds were analyzed to identify risk factors for delayed healing and to evaluate the effectiveness of muscle flap coverage. Three risk factors were identified: preoperative or postoperative radiation therapy, resection for recurrent carcinoma, and inflammatory bowel disease. A total of 19 muscle flaps (11 gracilis, five gluteal thigh, two gluteus maximus, and one rectus abdominis) were used to close these wounds. During an average 3.5-year follow-up, four (31%) minor complications and one (8%) recurrence were noted to occur. Muscle flaps provide safe, effective, single-stage procedures for the closure of chronic perineal wounds.

(*Arch Surg.* 1990;125:1371-1377)

Delayed healing of the perineum after proctectomy occurs in 7% to 40% of patients.[1-10] Half of these open perineal wounds fail to close within 6 months and up to a quarter remain open at 1 year.[4,7] These recalcitrant wounds, which occur most frequently in patients treated for rectal inflammatory bowel disease or carcinoma, are the most common late complication after proctectomy.[1] Chronic perineal wounds may persist for years, causing considerable morbidity. For many patients, the wounds are so painful that sitting is impossible. In addition, these wounds require daily care and their drainage is a source of annoyance and embarrassment. Finally, these wounds place patients at increased risk of local infection or systemic sepsis.

Once a perineal wound has become chronic, local wound care (including sitz baths and frequent dressing changes) is seldom successful, and further surgery is usually required.[1-3] Surgical procedures advocated for these wounds include débridement and curettage,[1] excision and primary closure,[2] and serial débridement with skin grafting.[9] These methods all require multiple procedures and a prolonged treatment period and are often unsuccessful, especially in the presence of radiation injury.[1,2,9,11,12] Wide unroofing (marsupialization) of the sinus via coccygectomy may be effective, but healing can take up to 2 years.[3]

The development of the muscle flap has provided an alternative treatment for problem wounds.[13] Wound débridement with immediate muscle flap closure has proved to be successful in the treatment of other chronic infected wounds, including osteomyelitis,[14] pressure sores,[15] and postoperative sternal infections.[15] Based on a review of patients treated for recalcitrant wounds of the perineum after proctectomy, we will (1) identify risk factors for delayed perineal wound healing, (2) analyze the effectiveness of muscle flap closure in the treatment of such wounds, and (3) propose treatment guidelines to provide quick and reliable closure of these wounds.

PATIENTS AND METHODS

The records of 13 consecutive patients who underwent muscle flap closure of chronic postproctectomy perineal wounds from 1979 through 1988 were reviewed. Chronic wounds were defined as those developing after primary perineal closure and persisting for more than 1 month despite local wound care.

The patient group included nine men and four women with an average age of 48 years. Their wounds had been present for an average of 42 months and averaged 44 cm^2 after operative débridement. Nine patients had undergone a total of 18 unsuccessful operations before the muscle flap procedure. These failed operations included débridement and curettage (14 operations in seven patients), débridement with primary closure (three operations in three patients), and débridement with partial coccygectomy (one patient).

At the time of the muscle flap procedure, patients underwent wide débridement of infected, nonviable, or fibrotic tissue, including any bone exposed in the wound. Débridement was followed by immediate muscle flap coverage using gracilis, gluteus maximus, inferior gluteal thigh, or rectus abdominis flaps. One patient with a perineal small-bowel fistula due to inflammatory bowel disease underwent débridement via combined abdominoperineal (AP) approach with immediate muscle flap closure. One patient who had previously received 500 Gy

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Table 1.—Wound Characteristics, Treatment Method, and Outcome in Patients With Recalcitrant Perineal Wounds

	Mean Wound Characteristics				Outcome	
Risk Category	**Size, cm²**	**Duration, mo**	**Prior Procedures**	**Muscle Flap (No.)**	**No. (%) of Minor Complications**	**No. (%) of Recurrences**
Radiation injury (n = 6)	42	30	1.2	Gracilis (4); gluteal thigh (5); gluteus maximus (1); rectus abdominis (1)	1 (17)	1 (17)
Recurrent carcinoma (n = 2)	16	38	1.0	Gracilis (3)	0	0
Inflammatory bowel disease (n = 5)	54	63	1.8	Gracilis (4); gluteus maximus (1)	3 (66)	0
Total	44	42	1.5	Gracilis (**11**); gluteal thigh (**5**); gluteus maximus (**2**); rectus abdominis (**1**)	4 (31)	1 (8)

of perineal irradiation underwent immediate muscle flap closure at the time of AP resection. The remaining patients underwent débridement and muscle flap closure after they developed chronic perineal wounds.

Follow-up evaluations were performed during subsequent clinic visits. At each visit, patients were asked whether they had experienced any perineal pain, and their wounds were examined for any recurrent drainage.

RESULTS

Patients who developed nonhealing perineal wounds after proctectomy can be divided into three risk groups: (1) preoperative or postoperative radiation therapy for rectal carcinoma (six patients), (2) resection for recurrent anal or rectal cancer (two patients), and (3) proctectomy for inflammatory bowel disease (five patients) (Table 1). One of the patients who underwent radiation therapy received preoperative therapy (15 Gy) and the other five received full-dose treatment (45 to 56 Gy) following AP resection.

In all patients, muscle flap closure initially resulted in a healed wound (average time to healing, 21 days). Four patients developed minor complications (three minor wound separations and one instance of prolonged drainage of seroma), which resolved with conservative management. There were no instances of flap loss or major complications requiring reoperation. The average duration of hospital stay was 14 days. During an average follow-up period of 3.5 years, 12 patients (92%) were asymptomatic without evidence of wound recurrence. One patient (8%) developed a late wound recurrence at 6 months. A combined AP approach was employed, and a rectus abdominis muscle flap was used to close this wound. This patient remains healed and asymptomatic 4 months postoperatively. One of the two patients with local carcinoma recurrence died of metastatic disease 8 months after muscle flap closure. All other patients were free of disease at the last follow-up visit.

COMMENT

We have identified three preoperative risk factors for the development of chronic perineal wounds after proctectomy: recurrent anal or rectal cancer, prior local radiation therapy, and inflammatory bowel disease. The increased risk of chronic perineal wounds in patients with recurrent anal or rectal cancer has not been previously reported, to our knowledge. The association of local radiation therapy and inflammatory bowel disease with increased risk of chronic perineal wounds is well known.[1,4-10,12,15,16]

Recurrent cancer, radiation therapy, and inflammatory bowel disease all lead to local fibrosis with diminished vascularity and impaired healing.[1,3,15] If perineal healing is sufficiently impaired by any of these conditions, a chronic wound will develop. Identification of patients at a high risk of impaired perineal healing enables the surgeon to better counsel such patients before surgery and to begin treatment promptly should a chronic wound develop.

For selected patients at risk of postoperative perineal wound breakdown (for example, patients with severe radiation injury or active perineal suppuration), careful consideration should be given to the use of a muscle flap closure immediately after completion of the rectal resection. In this series, immediate muscle coverage was used in one patient. Débridement with immediate muscle flap coverage is already well established in the treatment of other chronic infected wounds, such as osteomyelitis, sternal infections,[15] and pressure sores.[16] Immediate muscle or fasciocutaneous flap closure may be performed with minimal blood loss and without a change in the patient's position after completion of the AP resection.

In patients who develop chronic perineal wounds, nonoperative management, with a prolonged period of local wound care and oral antibiotic therapy, is generally unsuccessful.[1,3] These patients require surgical treatment. However, procedures such as excision and primary closure or débridement with skin grafting are successful in less than half of patients.[1,4,9] The ineffectiveness of these medical and surgical treatments is underscored by the histories of our patients. They had undergone an average of 1.5 previous operations, and yet their wounds were still present after an average of 42 months.

In an effort to achieve more rapid and reliable closure of these recalcitrant wounds, a treatment approach has been developed that includes a thorough wound analysis, followed by wound débridement and immediate muscle flap closure. To plan our operative procedure better, chronic wounds are evaluated by physical examination, wound culture, and magnetic resonance imaging, which is more helpful than sinography in the delineation of the extent of these wounds. Contrast evaluation of the gastrointestinal tract is performed in patients with inflammatory bowel disease or in whom a small-bowel–perineal fistula is suspected. If active inflammatory bowel disease is present, it is controlled medically before surgery. In all patients, nutritional status is optimized, and culture-specific antibiotics are administered.

Once the extent of the wound is known and the patient has been prepared for surgery, wound débridement is performed. Placement of a urethral catheter facilitates identification of the urethra during the perineal dissection. The injection of methylene blue into the perineal sinus allows determination of its extent. Biopsy specimens are submitted for examination to exclude recurrent carcinoma as the cause of the wound. With the use of a combination of sharp dissection and cautery, any infected, necrotic, or fibrotic tissue adjacent to the sinus is débrided. Near the peritoneal reflection, a curette is useful

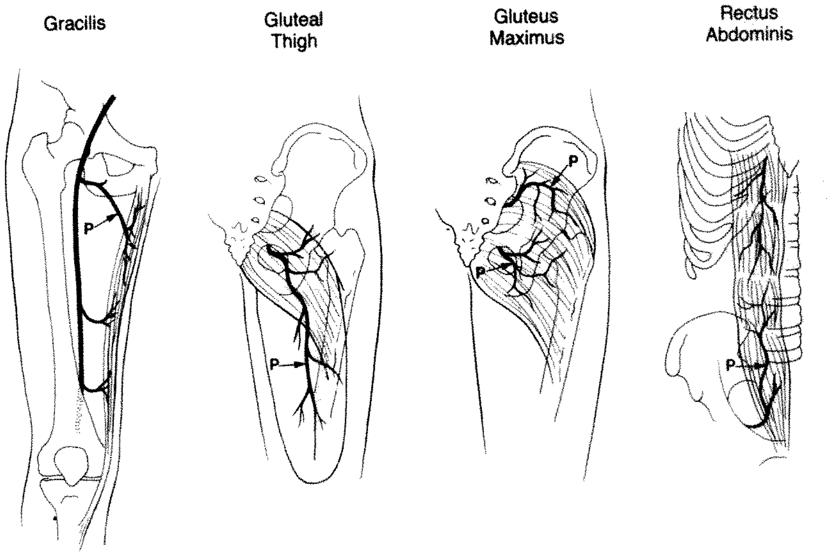

Fig 1.—Muscle flaps recommended for perineal reconstruction. Arrows indicate dominant vascular pedicle. p indicates the medial femoral circumflex vessels for the gracilis flap; the inferior gluteal vessels for the gluteal thigh flap; the superior and inferior gluteal vessels for the gluteus maximus flap; and the inferior epigastric vessels for the rectus abdominis flap.

Table 2.—Muscle Flap Selection for Perineal Wounds

	Chronic Wounds		Immediate Coverage	
Relative Preference	**Small Skin Defect**	**Large Skin Defect**	**Combined Abdominoperineal Approach**	**Perineal Approach Only**
1	Gracilis	Gluteal thigh	Rectus abdominis	Gluteal thigh
2	Gluteus maximus	Rectus abdominis*	Gluteal thigh	Gracilis
3	. . .	Gluteus maximus	Gracilis	. . .

*If combined abdominoperineal approach is used.

to avoid entering the peritoneal cavity. If the coccyx is exposed by the débridement, it is removed. For exceptionally large wounds or those where a bowel fistula may exist, simultaneous AP approaches may be required.

When débridement is complete, the wound is irrigated and a muscle flap is selected that will safely reach the perineal defect when elevated as a flap. When transposed into the débrided wound, the muscle flap provides the bulk to fill the débridement cavity and obliterate dead space, while providing well-vascularized tissue that is resistant to bacterial infection.[13-16] Muscle provides an improved blood supply for the wound, increasing oxygen tension[14,16] and improving leukocyte delivery and function.[17,18]

Only those muscles whose use will not produce functional impairment are used. The gracilis, gluteus maximus (inferior or superior half), gluteal thigh, and rectus abdominis muscle flaps are recommended for perineal reconstruction after wound débridement (Fig 1). When these muscles are used for muscle flaps, adjacent synergistic muscles preserve function.

The flap of choice depends on three factors: the muscle flaps available, the size of the wound, and the amount of skin required for closure (Table 2). Muscle flap availability is dependent on the patient's position during surgery, the status of each muscle's vascular pedicle, and the surgical approach to the wound (Fig 2). Dissection of the rectus abdominis must be done with the patient in the lithotomy position, while the gluteus maximus is accessible with the patient in the prone position only; the gracilis and gluteal thigh flaps may be dissected with the patient in either position. If a muscle's vascular supply has been interrupted (by either previous surgery or the débridement) the muscle cannot be used. Finally, the surgical approach to the perineal wound may limit the flaps available for use. For example, the rectus abdominis transposition to the perineum is preferable via the peritoneal

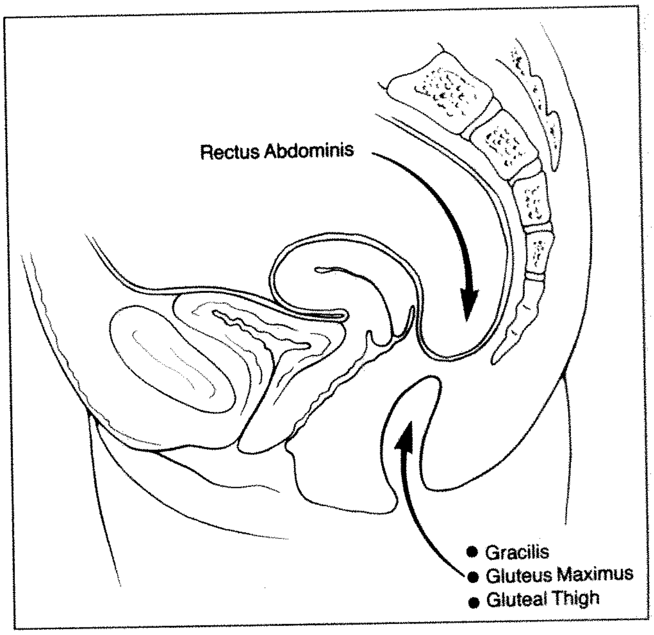

Fig 2.—Illustration of muscle flaps available depending on the surgical approach to the perineal wound.

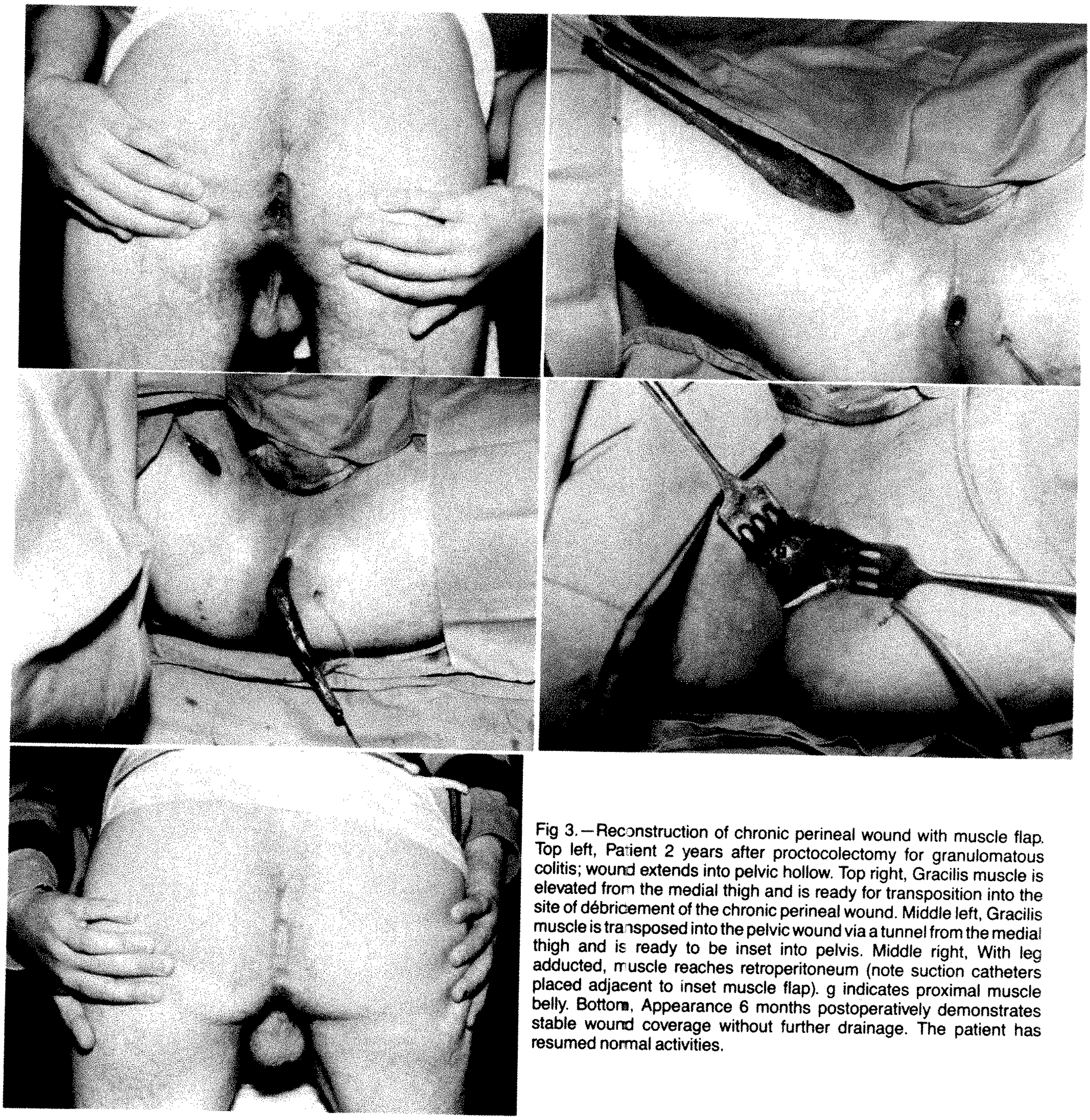

Fig 3.—Reconstruction of chronic perineal wound with muscle flap. Top left, Patient 2 years after proctocolectomy for granulomatous colitis; wound extends into pelvic hollow. Top right, Gracilis muscle is elevated from the medial thigh and is ready for transposition into the site of débridement of the chronic perineal wound. Middle left, Gracilis muscle is transposed into the pelvic wound via a tunnel from the medial thigh and is ready to be inset into pelvis. Middle right, With leg adducted, muscle reaches retroperitoneum (note suction catheters placed adjacent to inset muscle flap). g indicates proximal muscle belly. Bottom, Appearance 6 months postoperatively demonstrates stable wound coverage without further drainage. The patient has resumed normal activities.

cavity and should be used only after a combined AP approach.

The gracilis muscle flap is the flap of choice[13] for most chronic perineal wounds (Fig 3). Although it is possible to include skin in a gracilis flap,[13,19] most perineal wounds are not associated with skin deficiency. Furthermore, the inclusion of a skin island limits the degree to which the muscle can be rotated into the proximal retroperitoneal wound. For larger defects within the sacral hollow, both gracilis muscles may be used. Wounds that require skin coverage (ie, those in patients who have undergone preoperative or postoperative radiation therapy for rectal carcinoma and thus exhibit irradiated perineum with skin deficiency) may be closed with use of the gluteus maximus with a skin island.[13,20] Because of its dual circulation, it is possible to split the muscle and use either the inferior or superior half as a flap, leaving the remaining half intact to preserve function. The gluteal thigh flap, based on the descending branch of the inferior gluteal artery, can cover larger perineal defects[21,22] (Fig 4). Its primary use is in wounds with extensive skin defects (wounds that require immediate reconstruction or large radiation wounds). When primary or delayed perineal reconstruction is performed with the combined AP approach, the rectus abdominis muscle flap is recommended.[13] By incising the rectus sheath, the rectus abdominis muscle can be elevated via the same midline incision used to perform the AP resection. While the rectus abdominis can be tunneled subcutaneously, it covers a larger area when brought through the abdominal cavity into the perineal wound. Once the muscle has been inset into the débrided

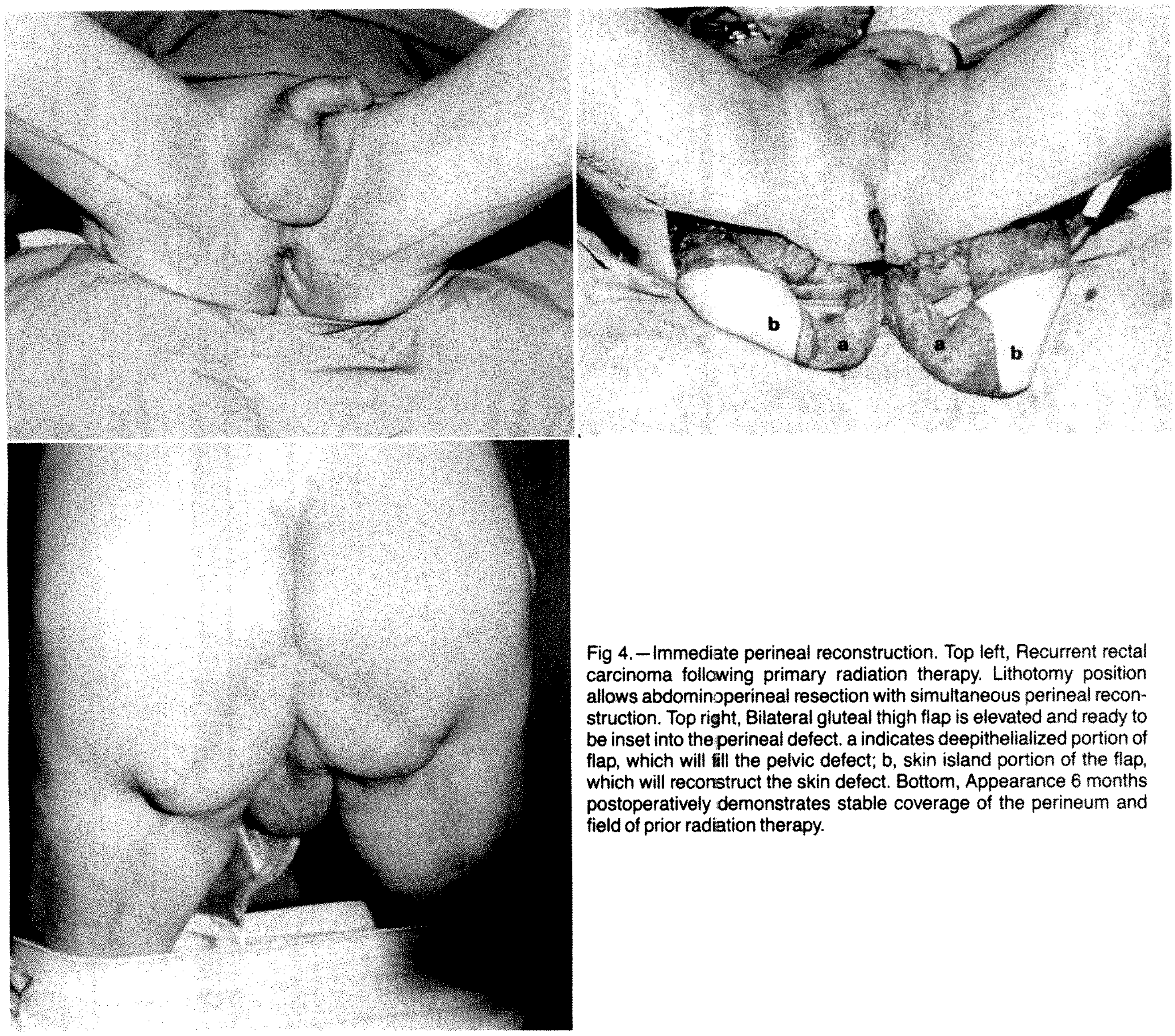

Fig 4.—Immediate perineal reconstruction. Top left, Recurrent rectal carcinoma following primary radiation therapy. Lithotomy position allows abdominoperineal resection with simultaneous perineal reconstruction. Top right, Bilateral gluteal thigh flap is elevated and ready to be inset into the perineal defect. a indicates deepithelialized portion of flap, which will fill the pelvic defect; b, skin island portion of the flap, which will reconstruct the skin defect. Bottom, Appearance 6 months postoperatively demonstrates stable coverage of the perineum and field of prior radiation therapy.

wound, the anterior rectus sheath is closed. While it is possible to develop a hernia at the site of rectus removal, careful closure of the anterior rectus sheath will minimize this complication. When the rectus has been transposed superiorly for breast reconstruction, the incidence of abdominal hernia is 2.1%.[23]

Although the omentum has been used to successfully cover a variety of infected wounds,[13] its use in perineal reconstruction is limited. The omentum is frequently either resected or placed in the pelvic inlet during the initial proctocolectomy. Access to the omentum requires celiotomy, and the omentum provides no skin coverage. The muscle flaps recommended have no such limitations and are preferred for closure of chronic wounds.

Once the muscle is inset into the wound, it is sutured into the débrided wound bed with the use absorbable sutures. Suction drains are placed in both the donor muscle site and the perineal wound. Culture-specific antibiotic therapy is administered for an average of 7 days with patients maintained at bedrest. Recovery is generally rapid, with patients discharged 7 to 14 days after surgery. Minor complications, such as small amounts of drainage or minor wound dehiscences, are treated conservatively with local wound care.

Utilization of débridement and muscle flap closure enables successful treatment of recalcitrant perineal wounds by a single procedure in 12 (92%) of 13 patients. The single perineal wound recurrence (in a patient with an extensive radionecrotic wound) has been successfully managed with repeated débridement and an additional muscle flap. Presently, all patients in our series have healed perineal wounds. The average time to healing (21 days) is less than reported with any other method of closure of chronic perineal wounds.

CONCLUSION

Prior perineal radiation, recurrent anal or rectal carcinoma, and inflammatory bowel disease each increase a patient's risk of chronic perineal wound development after proctectomy. For the majority of at-risk patients, careful follow-up is all that is required. For patients who develop chronic perineal wounds, débridement and muscle flap coverage will provide the most effective and expeditious treatment. Patients with severe skin injury secondary to radiation exposure or active perineal suppuration are especially likely to develop chronic perineal wounds after proctectomy. For such patients, immediate muscle flap closure at the time of proctectomy should be considered.

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Discussion

GEORGE A. HIGGINS, MD, Santa Barbara, Calif: With closer attention to patients' preoperative nutritional status and with proper antibiotic coverage, primary closure of the perineal incision is successful in almost all instances, even when the procedure is done for inflammatory bowel disease. Nevertheless, when healing has been impaired by radiation therapy or when large areas of perineum must be excised because of local recurrence, the closure techniques described are extremely useful. Dr Mathes is one of the pioneers in the use of muscle and musculocutaneous flaps, and these comparatively new techniques have been a great advance in difficult wound closure situations. One of the founding members of this society, Dr Samuel Robinson of Santa Barbara, first described the muscle flap procedure using the latissimus dorsi muscle for closure of chronic empyema cavities in 1916. Dr Robinson trained in Boston and was the first thoracic surgeon at the Mayo Clinic before moving to California shortly after World War I. He colorfully described the chronic open thoracic wound as "that patriarch of the surgical scrap heap," and the same might be applied to the nonhealing perineal wound for which Drs Mathes and Anthony have given us this most satisfactory solution.

ANTHONY SHAW, MD, Pasadena, Calif: This problem will likely be seen less frequently due to the use of continence-preserving procedures, which at the same time obliterate the possible perineal wound complication. The problem may continue, of course, in patients with Crohn's disease, which seems to be becoming more common as ulcerative colitis becomes less common.

In the 1970s, I performed a resection in a young girl who had toxic megacolon, and she subsequently had a chronic perineal sinus, which resisted all efforts to heal it, including coccygectomy, removal of the lower two sacral segments, marsupialization, etc. Because this patient's chronic cavity was large, we split the gluteus maximus in the direction of its fibers distally down toward the thigh, divided the medial portion distally, and rotated it up into this defect, filling the defect with a bulky muscle pedicled on the inferior gluteal vessels.

Have the authors performed dissection up the the gracilis muscle, found that it was really inadequate, ie, that it had a slim tendon, and then had to do something else?

We described this operation in *Surgery, Gynecology and Obstetrics* in 1978. Since then, Dr Jurkiewicz, chairman of plastic surgery at Emory University, has reported half a dozen or so cases where he employed this technique, using the medial portion of the gluteus maximus where the gracilis muscle failed to cure the chronic perineal sinus.

ALAN MORGAN, MD, Seattle, Wash: Surgeons who excise the rectum and anus have all been faced with this complication and will be faced with more such complications the more they deal with Crohn's disease.

I do think delayed healing may be achieved within 2 years. I would not give up and label the wound persistent; I prefer the word "recalcitrant." Steroid therapy may be discontinued, patients may put on some weight, and the surgeon can try many little tricks to achieve that final bit of healing: curettage may be performed to remove hair or irrigation with nitrogen mustard may also help a great deal. The real effort by surgeons, however, should be directed toward the achievement of primary healing. The patient must be in the optimum nutritional state with anemia corrected at the time of surgery; steroid therapy does not seem to be a factor here.

The surgeon must slow down, pay attention to detail, and get that closure just right at the end of the operation. There must be no mucosa left, and sphincters should be excised because saving muscles here does not really help. In Crohn's disease, it is best that muscles be excised. The suture should be soft as silk. The drains must be effective. Large closed wound suction drainage systems (Hemovacs) are best, and the surgeon should use two in case one of them becomes blocked. We must ask our nurses to prevent the skin from getting soggy during the postoperative period.

I would think that during the next couple of years, the authors' cases are going to double in number!

ERIC W. FONKALSRUD, MD, Los Angeles, Calif: During the past several years, as the endorectal ileal pull-through procedure has become more prominent as a method of treating patients with ulcerative colitis, we have observed that filling the perineal space with another portion of the intestine (the ileum) has tended to obliterate the pelvic space. Therefore, these patients who would ordinarily be subjected to a high risk of chronic perineal sinuses actually have a very low incidence of this complication.

Because of the high likelihood of a chronic perineal sinus developing after standard proctocolectomy in patients with inflammatory bowel disease, rather than use perineal drainage from below, we have changed the technique to closure of the perineal muscle, subcutaneous tissues, and skin from below with pelvic drainage for 4 or 5 days through the abdomen. We have subsequently observed a marked decrease in the incidence of chronic perineal wound sinuses. The problem appears to be in large part due to the pelvic space that needs to be filled, accentuated by the local inflammation associated with inflammatory bowel disease. We continue to use pelvic drainage from above in patients who do not undergo a pull-through procedure.

Dr Mathes, have any of your patients had drainage from above or has drainage been performed from below in all cases?

DR MATHES: Dr Higgins, surgeons must pay attention to the nutritional status of both the patient undergoing perineal resection and the patient who has a chronic perineal wound. In both instances, nutritional emphasis may well let these wounds heal without surgical intervention.

Dr Shaw, in 1978 you described use of the gluteus maximus muscle for closure of a chronic perineal wound. I would stress that the gluteus maximus is a substantial muscle that is functionally important in the maintenance of hip stability. As you suggested in your article, the muscle may be split using only half of it as a flap. Because this muscle has dual circulation, the superior and inferior gluteal arteries, it can be split, leaving half of it intact and without vascular injury. For the perineal region, usually the superior half is left intact, and the inferior half is rotated as a flap. The inferior half based on the inferior gluteal vascular pedicle reaches quite nicely into the perineal wound after release of its fibers of insertion.

The gracilis muscle is fairly small, although it is generally adequate for reconstruction of most perineal wounds. Once you elevate the muscle and tunnel it directly from the medial thigh into the perineal wound, you have increased its arc of rotation into the presacral defect. Furthermore, when you adduct a patient's leg after initial flap elevation in the lithotomy position, the muscle will reach all the way up to the perineal reflection without excessive tension on its vascular pedicle.

In the standard chronic perineal wound, there is usually a very small skin defect, so you do not really need a skin island with the muscle. It is probably a mistake to try to use a skin island with the gracilis muscle to avoid limiting its ability to turn into the sacral hollow where the muscle flap is necessary.

Both medial thighs are prepared so that we are able to use the bilateral gracilis muscle flaps if we believe that one gracilis muscle is not adequately filling the site of wound débridement.

Dr Morgan, your emphasis on careful wound closure at the time of total colectomy will generally prevent the chronic perineal wound in the first place. In our experience, if the wound is not healed by 6 months, it is time to consider a secondary procedure, such as débridement and muscle flap closure. A small-bowel follow-through procedure is performed to ensure the absence of concurrent small-bowel disease. This may require treatment before attempts at closure of the perineal wound.

Some of our patients had recurrent cancer. We do not hesitate to perform a biopsy before we perform a wound closure to make sure the patient does not have recurrent tumor.

Dr Fonkalsrud, drainage through the peritoneal cavity may be better to obtain a healed wound at the time of AP resection. In the majority of our patients, we utilize the perineal approach and are careful to ensure closed-suction drainage to help approximate the muscle to the sacral wall.

In the patient in whom primary radiation therapy for rectal carcinoma has failed, there is a very high risk for the development of a chronic perineal wound. In such patients, we advocate a combined approach—AP resection and muscle flap closure. In such cases, we prefer to use the rectus abdominus muscle with the peritoneal approach.

Hypertensive Black Men and Women: Quality of Life and Effects of Antihypertensive Medications

Sydney H. Croog, PhD; B. Waine Kong, PhD; Sol Levine, PhD; Matthew R. Weir, MD; Robert M. Baume, PhD; Elijah Saunders, MD; the Black Hypertension Quality of Life Multicenter Trial Group

A multicenter, randomized double-blind clinical trial was conducted among 306 black men and women with mild to moderate hypertension to determine effects of atenolol, captopril, and verapamil SR on measures of quality of life. Patients were randomly assigned to a stable or forced-dose titration sequence. After an 8-week treatment period, the rate of withdrawal from treatment because of adverse effects was low and did not differ by drug treatment group or titration level. Patients taking verapamil SR showed a significantly greater reduction in mean blood pressures than patients treated with atenolol or captopril. Along with absence of worsening on any quality of life total scale scores examined over the treatment period, we found either improvement or no change in the total scale scores for all three treatment groups. Among both male and female patients, comparisons *between* drug treatment groups showed no differences in degree of change on the total scale scores. In comparisons *within* each treatment group, improvement in scores of male patients after 8 weeks appeared among those taking atenolol in general well-being and physical symptoms reduction; among male patients taking captopril in general well-being, physical symptoms, and sexual performance; and among male patients receiving verapamil SR in scores in irritability, sleep, and the Digit Span test. Improvement in scores among female patients taking atenolol was found in scores on general well-being, physical symptoms, and sleep; among women taking captopril on general well-being, physical symptoms, and irritability; and among women taking verapamil SR on general well-being. Patients in all treatment groups improved on measures of visuomotor functioning. The research shows that with the three newer generation antihypertensive medications studied, blood pressure control was achieved during the treatment period without negative effects on quality of life scales, along with findings of improvement on some measures. Given the special clinical features of hypertension in black patients, the study underlines as well the potential and utility of systematic tracking of measures of quality of life, while monitoring blood pressures in this patient population (*Arch Intern Med.* 1990;150:1733-1741).

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Fibrin Glue Inhibits Intra-abdominal Adhesion Formation

Christian de Virgilio, MD; Terry Dubrow, MD; Barry B. Sheppard, MD; William D. MacDonald, MD;
Ronald J. Nelson, MD; Malcolm A. Lesavoy, MD; John M. Robertson, MD

• To determine the effect of fibrin glue on intra-abdominal adhesion formation, 45 rats were randomized to three groups. Each animal received two adhesion models. Group 1 received no further treatment. Groups 2 and 3 had the adhesion models covered with fibrinogen from fresh frozen plasma (1.77 g/L) and cryoprecipitate (23.6 g/L), respectively. In group 1, 13 of 15 rats had high-grade adhesions in both models. In group 2, high-grade adhesions were noted in nine of 15 rats in model 1 and in 12 of 15 rats in model 2. In group 3, however, high-grade adhesions were seen in only three of 15 rats in model 1, with 11 rats having no adhesions, and in only two of 15 rats in model 2. Histologic analysis suggested accelerated healing in group 3. We conclude that (1) fibrin glue inhibits intra-abdominal adhesion formation in rats, (2) the inhibitory action is dependent on the fibrinogen concentration of the fibrin glue, and (3) adhesions are reduced by fibrin glue regardless of whether the peritoneal defect is closed.

(*Arch Surg.* 1990;125:1378-1382)

The use of fibrin glue (FG) in surgery to seal vascular anastomoses and prostheses and to control local bleeding is increasing.[1] Recently, FG was used in hepatic and splenic trauma to control hemorrhage.[2] It is particularly useful in patients with coagulation or platelet disorders, since FG does not depend on adequate platelet or clotting factor levels or function.[2]

Fibrin glue is made by mixing a source of highly concentrated fibrinogen with thrombin, calcium, and factor XIII. The source of fibrinogen can be from either lyophilized pooled concentrated human fibrinogen (Tisseel Kit, Immuno AG, Vienna, Austria) or single donor human cryoprecipitate. The thrombin is generally of bovine origin. This fibrin glue dispersion system is not yet approved in the United States for general clinical use because of the concerns of it being a pooled blood product.

Previous studies have suggested that FG may decrease intra-abdominal adhesion formation, although the mechanism is not known.[3,4] These studies have all used the lyophilized pooled fibrinogen. In this study, FG prepared from cryoprecipitate was used to test its effect on intra-abdominal adhesion formation in rats with the use of two different adhesion models. Furthermore, two different concentrations of fibrinogen were used to see if any inhibition was concentration dependent. Finally, histologic analysis was performed to compare wound healing and the inflammatory response with and without FG sealant.

MATERIALS AND METHODS

Forty-five Sprague-Dawley rats weighing 250 to 350 g were used in the study. General anesthesia was induced using a mixture of ketamine hydrochloride and xylazine hydrochloride given intraperitoneally. A midline laparotomy was then performed.

To the left and right of midline, standard circular 1.5-cm-diameter, peritoneal-muscular defects were excised. On the right side, the defects were closed linearly using four interrupted 3-0 silk sutures as previously described.[3] On the left side, the defects were left open, and a continuous 3-0 suture was sewn circumferentially around the wound (a model developed by one of us [M.A.L.]; unpublished data). The rats were then randomized into three groups as follows: in group 1, no further treatment was administered and the laparotomy incision was closed with a running 3-0 suture (Dexon, Davis and Geck Inc, Manati, PR). In group 2, each defect was covered with a mixture of 0.1 mL of human fibrinogen (1.77 g/L) obtained from fresh frozen plasma activated with 0.1 mL of bovine thrombin (1000 U/mL) and calcium (6.24 mmol/L). The sealant was allowed to set for 4 minutes, which yielded a soft gelatinous plug, and then the laparotomy incision was closed with the running 3-0 suture. In group 3, each defect was covered with 0.1 mL of human fibrinogen (23.6 g/L) obtained from cryoprecipitate mixed with 0.1 mL of bovine thrombin (1000 U/mL) and calcium (6.24 mmol/L). After allowing the sealant to set for 4 minutes, which yielded a firm gelatinous plug, the laparotomy was likewise closed with the 3-0 sutures.

The rats were maintained for 7 days with food and water ad libitum. On the seventh postoperative day, they were killed using a lethal dose of intraperitoneal pentobarbital sodium. The laparotomy incision was opened and the degree of adhesion formation was graded from 0 to 4 by a "blinded" independent observer as follows: grade 0, no adhesions; grade 1, adhesions involving less than 25% of the area; grade 2, adhesions involving more than 25% but less than 50% of the area; grade 3, adhesions involving more than 50% but less than 75% of the area; and grade 4, adhesions involving more than 75% of the area.

Statistical analysis was performed using the Pearson χ^2 test. Six separate analyses were performed. For right-sided defects, group 1 was compared with group 2 using group 1 as a row and group 2 as a

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Read before the 61st Annual Meeting of the Pacific Coast Surgical Association, Laguna Niguel, Calif, February 21, 1990.

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Number of Rats in Each Adhesion Class*

Group	Grade 0	1	2	3	4
Right Side†					
1 (control)	2	0	0	7	6
2 (FFP)	1	2	3	4	5
3 (FG)‡	11	1	0	1	2
Left Side§					
1 (control)	1	0	1	2	11
2 (FFP)	0	3	0	1	11
3 (FG)‖	0	7	6	1	1

*FFP indicates fresh frozen plasma; FG, fibrin glue.
†Defect closed with interrupted sutures.
‡*P*<.01 vs group 1 and *P*<.01 vs group 2.
§Defect left open and circumferential suture placed.
‖*P*<.001 vs group 1 and *P*<.01 vs group 2.

row, and using for columns the number of animals in each grade (0 to 4) (Table). This assessed for similarity of the distribution of adhesion ratings between the two groups. Next, group 1 was compared with group 3, then group 2 was compared with group 3 for the right-sided defects. The left-sided defects were then similarly analyzed comparing group 1 with group 2, then group 1 with group 3, and finally group 2 with group 3.

A second series of 24 Sprague-Dawley rats was studied for sequential histologic analysis to compare a control group of rats with rats treated with high-concentration fibrinogen FG. Following the creation of the same bilateral adhesion models, the rats were randomized into two groups of 12 corresponding to the control group (group 1) and the high-concentration fibrinogen group (group 3) of the initial series, so that in group A, no further treatment was given after creation of the bilateral defects. In group B, both the right- and left-sided defects were covered with a mixture of 0.1 mL of human fibrinogen (23.6 g/L) obtained from cryoprecipitate activated by 0.1 mL of bovine thrombin (1000 U/mL) and calcium (6.24 mmol/L). The rats were maintained with food and water ad libitum. Three rats from each group were killed at random on postoperative days 1, 3, 5, and 7 using a lethal dose of intraperitoneal pentobarbital. The laparotomy incision was opened and the entire right- and left-sided surgical defects were excised en bloc along with any adherent tissues. The specimens were fixed in formaldehyde solution, embedded in paraffin, and stained with hematoxylin-eosin and Masson trichrome stains.

RESULTS

The Table shows the number of rats in each adhesion class for the first series of 45 rats. On the right side (in which the peritoneal-muscular defects were closed with interrupted sutures), 13 of 15 rats in the control group had either grade 3 or 4 adhesions (Fig 1), and two had no adhesions. In group 2 (low-concentration fibrinogen from fresh frozen plasma), nine of 15 rats had grade 3 or 4 adhesions on the right side, and one had no adhesions. In group 3 (high-concentration fibrinogen from cryoprecipitate), only three of 15 rats had grade 3 or 4 adhesions and 11 had no adhesions (Fig 2). There was no statistical difference in the degree of adhesions between groups 1 and 2. Group 3, however, was significantly different (*P*<.01) from both groups 1 and 2.

On the left side (in which the peritoneal-muscular defects were left open and a continuous suture was placed circumferentially around the defect), 13 of 15 rats in group 1 (control) had grade 3 or 4 adhesions (Fig 3). In group 2, 12 of 15 rats had grade 3 or 4 adhesions. In group 3, only two of 15 rats had grade 3 or 4 adhesions (Fig 4). There was no statistically significant difference between groups 1 and 2. Group 3 was highly statistically different from group 1 (*P*<.001) and from group 2 (*P*<.01).

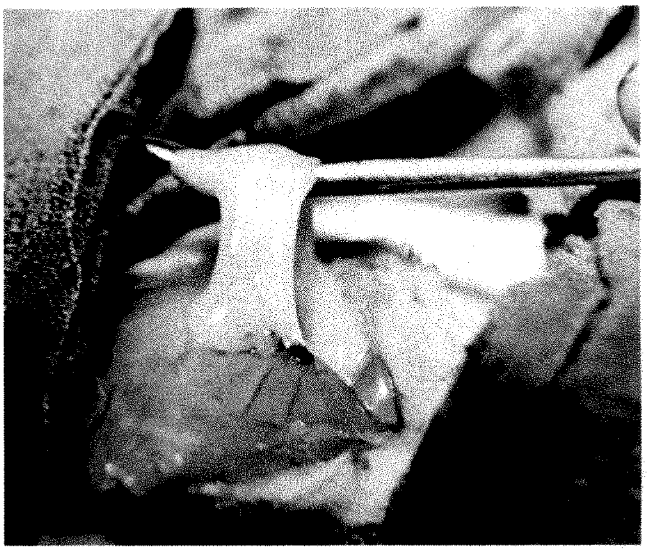

Fig 1.—Control group 1, right side of the peritoneum. A grade 4 omental adhesion can be seen involving the entire surface area of the closed defect on postoperative day 7.

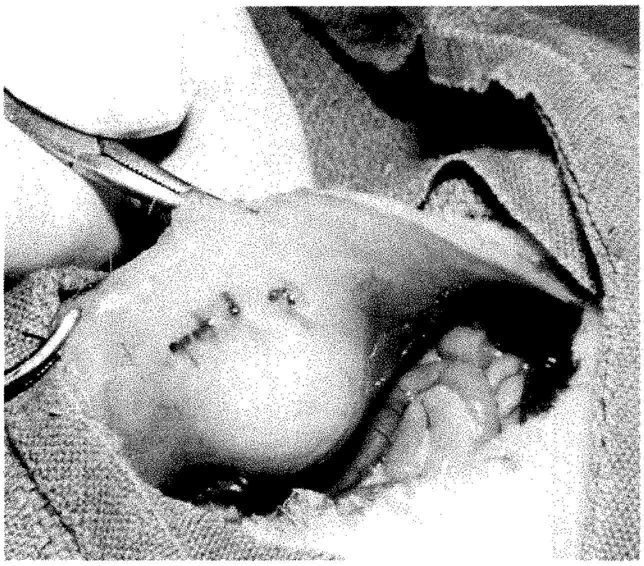

Fig 2.—Group 3, right side of the peritoneum. No adhesions are evident on postoperative day 7. The closed defect appears to be well healed.

The results from the second series of 24 rats were evaluated histologically. In group A (control group), polymorphonuclear leukocytes (PMNs) were the predominant cells seen in the wound surface on postoperative day 1. By postoperative day 3, numbers of PMNs were greatly diminished, macrophages were more prevalent, and early fibroblast proliferation with collagen deposition could be observed. Fibroblasts were widely proliferating by day 5 and neovascularization was becoming prominent. On day 7, fibroblastic proliferation with collagen fiber deposition and prominent capillary formation was present (Fig 5).

In group B (high-concentration fibrinogen FG), a layer of fibrin could be seen covering skeletal muscle on the wound surface where the peritoneal-muscular defect had been excised. Scattered PMNs were likewise seen. On postoperative day 3, the cellular response and collagen deposition were similar to the control group. Residual fibrin was still present. By day 5, the majority of the fibrin had disappeared, and a

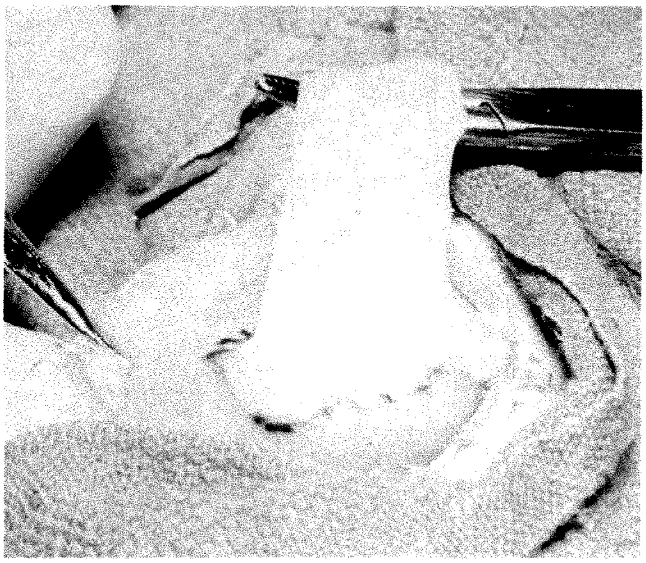

Fig 3.—Control group 1, left side of the peritoneum. A grade 4 omental adhesion can be seen involving the entire surface area of the open peritoneal defect.

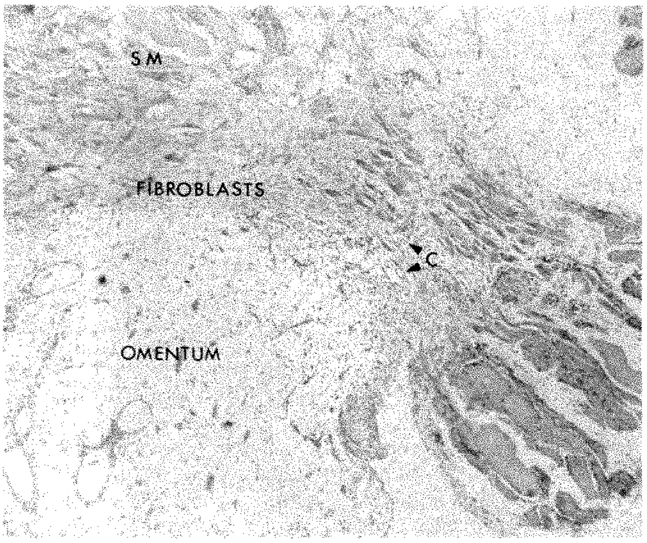

Fig 5.—Group A (control), postoperative day 7. Adherent adipose tissue (omentum) can be seen attached to skeletal muscle (SM). Fibroblastic proliferation with new capillary formation (C) is present at the interface between omentum and skeletal muscle (hematoxylin-eosin, ×4).

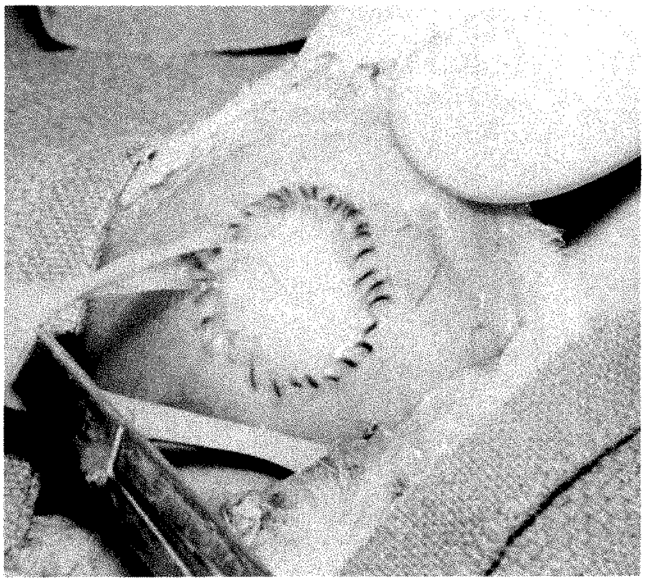

Fig 4.—Group 3, left side of the peritoneum. A grade 1 adhesion is demonstrated involving only one small area of the entire peritoneal defect.

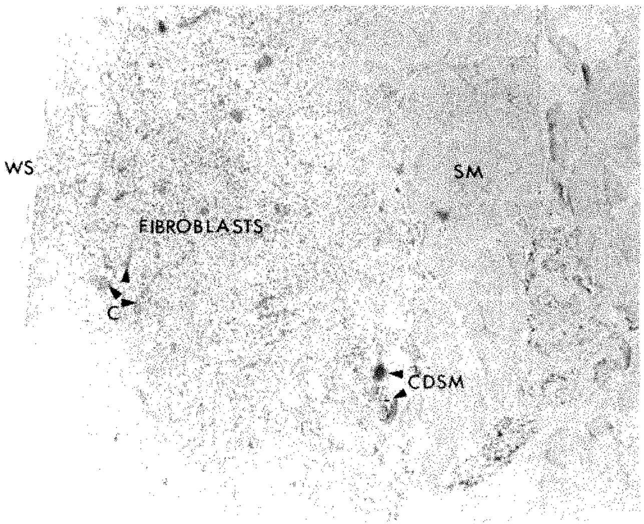

Fig 6.—Group B (fibrin glue), day 7. A marked fibroblastic response is present overlying the skeletal muscle (SM) with prolific ingrowth of new capillaries (C). Calcified degenerated skeletal muscle (CDSM) fibers are visible. Note that there is no tissue adherent to the wound surface (WS) (hematoxylin-eosin, ×4).

marked fibroblastic response was present along with occasional degenerating skeletal muscle fibers and foreign body giant cells. On day 7, the fibroblastic response with collagen deposition was even more prolific, as was the ingrowth of new capillaries (Fig 6). Calcified degenerated skeletal muscle fibers were abundant with associated foreign body giant cells. The capillary and fibroblastic response on day 7 appeared to be greater in the FG specimens than in the controls and was more consistent with healthy wound healing than adhesion formation as no adherent tissue suggestive of an adhesion was present in any of the day 7 specimens.

COMMENT

With the increasing concern over the use of homologous blood products, surgeons have focused on achieving better hemostasis intraoperatively. This has led to the development of numerous hemostatic agents. Because FG contains all the components of the last stage of the clotting cascade, FG achieves local hemostasis despite the presence of coagulation disorders, heparinization, or platelet disorders.[2] As such, it is especially useful in patients with dilutional coagulopathy who have sustained trauma or in vascular procedures requiring systemic heparin. Applied topically, it has been shown to decrease postoperative blood loss and the need for reoperation for bleeding after cardiac operations.[5]

Because FG is being used increasingly in surgery, it is important to know what effect FG may have on adhesion formation. In a series of experiments, Ellis[6] demonstrated that intra-abdominal adhesions form in response to ischemic tissue. His studies showed that neither the creation of a peritoneal defect alone nor the placement of loosely sutured black silk onto the parietal peritoneum induced adhesions. Adhesions formed when the peritoneal defect was closed, bringing tissue edges together and creating ischemia. These studies provided the basis for our model on the right side of the rat peritoneum. Additionally, we created a new model, designed by one of us (M.A.L., January 1987), in which the peritoneal defect was left open, but a continuous suture was placed circumferentially around the edge of the defect to maximize tissue ischemia. This new model appeared to cause even greater adhesion formation and thus provided a good control for our study.

The pathogenesis of intra-abdominal adhesion formation has also been studied histologically. Milligan and Raftery[7] demonstrated that on postoperative day 1, the viscera are joined by a network of fibrin containing predominantly PMNs in addition to lymphocytes, macrophages, and plasma cells. These early adhesions are fibrinous. By day 4, most fibrin has disappeared, and the predominant cell is the macrophage with a few fibroblasts. By day 5, the adhesions are formed by fibroblasts and collagen is present. At this stage, the adhesions are fibrous. Our study confirmed these histologic findings.

Since the deposition of fibrin is integral to the formation of adhesions, one would expect an increase in adhesion formation using FG. In fact, previous research has focused on the prevention of fibrin deposition. However, some studies have demonstrated a decrease in adhesion formation with FG. Lindenberg et al,[3] using a similar rat model as the right-sided defects in our series, demonstrated a significant reduction in adhesions using pooled lyophilized fibrinogen as the source of FG. In their study, aprotinin, an antiplasminogen agent, was added to the FG. The addition of aprotinin was thought to prolong the presence of the fibrin. Oka et al[4] studied the effect of FG on the leakage rate of rectal anastomoses in dogs. They similarly used pooled lyophilized fibrinogen and aprotinin and found that although the leakage rate was not different in the FG group vs controls, adhesions were significantly reduced in the FG group.

The present study confirms that FG significantly reduces intra-abdominal adhesion formation. This study differs in several respects from others in which FG was used. We used two different models for inducing adhesions. Fibrin glue significantly reduced adhesions in both models. In addition, we used single-donor products, fresh frozen plasma and cryoprecipitate, as the source of fibrinogen rather than pooled human blood, and we did not add antiplasminogen to the glue. Furthermore, by using fresh frozen plasma and cryoprecipitate, we were able to test two different concentrations of fibrinogen. Interestingly, the low-concentration glue (from fresh frozen plasma) did not reduce adhesions, suggesting that the inhibitory action of FG is dependent on the fibrinogen concentration. We cannot, however, exclude other components in the cryoprecipitate as being responsible for the inhibition of adhesions. Furthermore, the low-concentration glue did not form the typical solid gel seen with the higher concentration. This suggests that the greater sealant property of the high-concentration FG may play a role in adhesion prevention.

The FG used in our study has advantages over the dispersion kit used in Europe. The concentrated fibrinogen for our FG can be prepared from autologous single-donor cryoprecipitate using a method previously described, although with present techniques, this may require removal of 1 U of blood.[8] Thus, one avoids using a commercially prepared fibrinogen concentrate from a pooled human blood source with the attendant risks of hepatitis B and acquired immunodeficiency syndrome.

The reason for the inhibitory action of FG on adhesion formation is unclear. However, we believe that it is most likely due to the separation of raw surfaces created by the rapid sealant effect of the FG. This may prevent the exudation of substances from the ischemic wound that induce omentum and bowel surfaces to adhere and fibrous adhesions to form. Our histologic analysis suggests that FG does not inhibit fibroblastic proliferation. In fact, the fibroblastic and capillary response may have been increased with FG, although the observed histologic difference in our study was not statistically significant given the small number of animals studied per group. Previous studies support our findings and indicate that FG promotes the formation of granulation tissue, induces angiogenesis, and may thus accelerate healing.[9,10] The fact that FG may heighten fibroblastic proliferation and yet decrease adhesions suggests that other factors come into play in the formation of adhesions.

Nancy Berman, PhD, gave assistance with the statistical analyses involved in this project.

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Discussion

JONATHAN R. HIATT, MD, Los Angeles, Calif: During the past 100 years, a great deal of thought and effort have been devoted to the cause and prevention of adhesions. Causes that have been implicated include the presence of raw serosal defects, ischemia, foreign bodies such as talc, and inflammation. Preventive measures that have been tested and mostly abandoned include anticoagulants, steroids, high-molecular-weight substances such as dextran, and mechanical methods to stimulate intestinal motility and to prevent coaptation of healing surfaces. Tissue ischemia seems to have withstood the test of time as a cause of adhesions. However, the deleterious effect of fibrin deposition, which ought to produce adhesions, has been called into question. In a metaphor that becomes perplexing in light of the current presentation, Dr Harold Ellis, a great expert, has referred to fibrin as "nature's glue" and proposed its removal as a logical means to prevent loops of intestine from sticking. Now the authors reiterate the importance of ischemia but tell us that glue made from fibrinogen may have a preventive role in adhesion formation. Should we paint our anastomoses with this glue? The authors have not proposed a clinical application, but one concern would be the potential for infection. Fibrin trapping has been implicated in abscess formation after bacterial peritonitis, and fibrinolytic agents, including tissue plasminogen activator, have been used to prevent abscesses experimentally. Clinical trials using FG as a hemostatic sealant have not reported bacterial infection as a complication, but most of these cases, while wet, have been clean. Would use of the glue after an intraperitoneal inflammatory process of the sort likely to produce adhesions, for example perforative appendicitis, be a problem?

JAMES W. HOLCROFT, MD, Sacramento, Calif: Histologically, did the glue affect wound healing in any way? In terms of follow-up, if these areas form a new serosa over the inflammatory area, will adhesions ever form between the wounds and the omentum or the gut? If wound healing was impaired in any way, the long-term results might not have been quite so favorable.

LEON MORGENSTERN, MD, Los Angeles: As a long-standing student of adhesions in both rats and humans, I am equally impressed with the quixotic nature of adhesions in both species, sometimes mysteriously present and very often mysteriously absent. I find it difficult to relate this experimental procedure to what we see in man generally, and I would be very wary lest it be adopted as a means of preventing the adhesive phenomena we see in man. I did not hear mention of the risks of transmitting hepatitis, cytomegalovirus, or acquired immunodeficiency syndrome, when FG is applied in this fashion. I would appreciate hearing the authors' comments on that problem.

WILLIAM S. FLETCHER, MD, Portland, Ore: I remember a very convincing article that correlated the level of fibrinolysis with adhesions; the greater the fibrinolysis, the less the adhesions. Can the FG stimulate fibrinolysis?

DR NELSON: As a cardiac surgeon, I have been faced with many serious problems of hemostasis, particularly in operations that have to be "redone." One such instance is when the pump has depleted coagulation factors and the bleeding will not stop. Fibrin glue has been shown to be very helpful in this setting.

However, we questioned whether we were creating greater problems in the future if pericardial adhesions were stimulated. Would redone cardiac operations be more difficult? For that reason, Drs Robertson, who conceived this research, and de Virgilio took this problem to the laboratory and used a standard rat model for the study of adhesions. There is a problem as to how to relate this to man. The open defect was an additional model conceived by one of us (M.A.L.) in which a circumferential suture is used to increase ischemia to make it more productive of adhesions. The result that adhesions were reduced was a bit of a surprise to us, but this has been substantiated by other research work.

Dr Hiatt, what we may be seeing is a very simple but elegant biologic dressing over the surface of the peritoneum that allows the mesothelial cells to approximate to each other, and by the time fibrinolysis occurs, we have a smooth surface that no longer is susceptible to adhesion formation. It may also minimize the release of chemotactic factors.

One of us (T.D.) and Samuel E. Wilson, MD, in unpublished studies (January 1988), have shown that control animals did as well as the animals treated with fibrin. At high levels of contamination, the fibrin was not protective. However, at middle ranges of bacterial concentration, there was a statistically significant protective effect from the fibrin that localized the infection compared with the control.

In general surgery, the potential applications are limited only by one's imagination. Dr Shoemaker (Martin Luther King Medical Center, Los Angeles) and his group have applied it experimentally to the liver and the spleen in cases of trauma and splenectomy. It has been used to seal bowel anastomoses.

Dr Morgenstern, there clearly is a risk. The risk of hepatitis in Los Angeles County (California) now runs about 1% for each unit of blood or blood products that is transfused. The risk of acquired immunodeficiency syndrome runs about 1 in 75 000 to 1 in 250 000. We do not advocate using it unless there is a significant reason. In the event of bleeding, FG may decrease the risk by decreasing the total number of units transfused. We are working on plasmapheresis so one can take the product from the patient. Of course, genetic recombination production of fibrinogen is on its way.

Dr Fletcher, does this stimulate fibrinolysis? We do not know, but some European workers have used antifibrinolysis with this product, and it does not seem to add anything to its effect.

In Other AMA Journals

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Bacterial Transference During Electrodesiccation and Electrocoagulation

Richard G. Bennett, MD, Craig A. Kraffert, MD

Electrodesiccation and electrocoagulation are commonly used to control bleeding and destroy tissue. In certain outpatient settings, the clinician routinely uses one of these electrosurgical modalities on successive patients without sterilization or antisepsis of the treatment electrode tip. In controlled laboratory experiments using electrodesiccation and electrocoagulation, we investigated bacterial transference of *Staphylococcus aureus* from inoculated tissue to sterile electrode tips and from inoculated electrode tips to sterile tissue. With use on inoculated tissue, sterile electrode tips remained sterile after electrocoagulation but not after electrodesiccation. Bacterial transference from inoculated electrode tips to sterile tissue occurred with electrodesiccation but not with electrocoagulation. These results are consistent with bacterial destruction by electric current and suggest that bacterial transference via the treatment electrosurgery electrode from one patient to another is possible but much more probable during electrodesiccation than during electrocoagulation (*Arch Dermatol.* 1990;126:751-755).

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CONTRAINDICATIONS: ERGAMISOL (levamisole hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or its components.

WARNINGS: ERGAMISOL (levamisole hydrochloride) has been associated with agranulocytosis, sometimes fatal. The onset of agranulocytosis is frequently accompanied by a flu-like syndrome (fever, chills, etc.); however, in a small number of patients it is asymptomatic. A flu-like syndrome may also occur in the absence of agranulocytosis. It is essential that appropriate hematological monitoring be done routinely during therapy with ERGAMISOL and fluorouracil. Neutropenia is usually reversible following discontinuation of therapy. Patients should be instructed to report immediately any flu-like symptoms.

Higher than recommended doses of ERGAMISOL may be associated with an increased incidence of agranulocytosis, so the recommended dose should not be exceeded.

The combination of ERGAMISOL and fluorouracil has been associated with frequent neutropenia, anemia and thrombocytopenia.

PRECAUTIONS: Before beginning this combination adjuvant treatment, the physician should become familiar with the labeling for fluorouracil.

Information for Patients: The patient should be informed that if flu-like symptoms or malaise occurs, the physician should be notified immediately.

Drug Interactions: ERGAMISOL (levamisole hydrochloride) has been reported to produce "ANTABUSE®"-like side effects when given concomitantly with alcohol. Concomitant administration of phenytoin and ERGAMISOL plus fluorouracil has led to increased plasma levels of phenytoin. The physician is advised to monitor plasma levels of phenytoin and to decrease the dose if necessary.

Laboratory Tests: On the first day of therapy with ERGAMISOL/fluorouracil, patients should have a CBC with differential and platelets, electrolytes and liver function tests performed. Thereafter, a CBC with differential and platelets should be performed weekly prior to each treatment with fluorouracil with electrolytes and liver function tests performed every 3 months for a total of one year. Dosage modifications should be instituted as follows: If WBC is 2500-3500/mm^3 defer the fluorouracil dose until WBC is $>$ 3500/mm^3. If WBC is $<$ 2500/mm^3, defer the fluorouracil dose until WBC is $>$ 3500/mm^3; then resume the fluorouracil dose reduced by 20%. If WBC remains $<$ 2500/mm^3 for over 10 days despite deferring fluorouracil, discontinue administration of ERGAMISOL. Both drugs should be deferred unless enough platelets are present ($\geq$ 100,000/mm^3).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate animal carcinogenicity studies have not been conducted with levamisole. Studies of levamisole administered in drinking water at 5, 20, and 80 mg/kg/day to mice for up to 18 months or administered to rats in the diet at 5, 20, and 80 mg/kg/day for 24 months showed no evidence of neoplastic effects. These studies were not conducted at the maximum tolerated dose, therefore the animals may not have been exposed to a reasonable drug challenge. No mutagenic effects were demonstrated in dominant lethal studies in male and female mice, in an Ames test, and in a study to detect chromosomal aberrations in cultured peripheral human lymphocytes.

Adverse effects were not observed on male or female fertility when levamisole was administered to rats in the diet at doses of 2.5, 10, 40, and 160 mg/kg. In a rat gavage study at doses of 20, 60, and 180 mg/kg, the copulation period was increased, the duration of pregnancy was slightly increased, and fertility, pup viability and weight, lactation index, and number of fetuses were decreased at 60 mg/kg. No negative reproductive effects were present when the offspring were allowed to mate and litter.

Pregnancy: Pregnancy Category C: Teratogenicity studies have been performed in rats and rabbits at oral doses up to 180 mg/kg. Fetal malformations were not observed. In rats, embryotoxicity was present at 160 mg/kg and in rabbits, significant embryotoxicity was observed at 180 mg/kg. There are no adequate and well-controlled studies in pregnant women and ERGAMISOL should not be administered unless the potential benefits outweigh the risks. Women taking the combination of ERGAMISOL and fluorouracil should be advised not to become pregnant.

Nursing Mothers: It is not known whether ERGAMISOL is excreted in human milk; it is excreted in cows' milk. Because of the potential for serious adverse reactions in nursing infants from ERGAMISOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ERGAMISOL in children have not been established.

ADVERSE REACTIONS: Almost all patients receiving ERGAMISOL (levamisole hydrochloride) and fluorouracil reported adverse experiences. Tabulated below is the incidence of adverse experiences that occurred in at least 1% of patients enrolled in two clinical trials who were adjuvantly treated with either ERGAMISOL or ERGAMISOL plus fluorouracil following colon surgery. In the larger clinical trial, 66 of 463 patients (14%) discontinued the combination of ERGAMISOL plus fluorouracil because of adverse reactions. Forty-three of these patients (9%) developed isolated or a combination of gastrointestinal toxicities (e.g. nausea, vomiting, diarrhea, stomatitis and anorexia). Ten patients developed rash and/or pruritus. Five patients discontinued therapy because of flu-like symptoms or fever with chills; ten patients developed central nervous system symptoms such as dizziness, ataxia, depression, confusion, memory loss, weakness, inability to concentrate, and headache; two patients developed reversible neutropenia and sepsis; one patient because of thrombocytopenia; one patient because of hyperbilirubinemia. One patient in the ERGAMISOL plus fluorouracil group developed agranulocytosis and sepsis and died.

In the ERGAMISOL alone arm of the trial, 15 of 310 patients (4.8%) discontinued therapy because of adverse experiences. Six of these (2%) discontinued because of rash, six because of arthralgia/myalgia, and one each for fever and neutropenia, urinary infection, and cough.

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Adverse experience	ERGAMISOL N = 440 %	ERGAMISOL plus fluorouracil N = 599 %
Gastrointestinal		
Nausea	22	65
Diarrhea	13	52
Stomatitis	3	39
Vomiting	6	20
Anorexia	2	6
Abdominal pain	2	5
Constipation	2	3
Flatulence	<1	2
Dyspepsia	<1	1
Hematological		
Leukopenia		
<2000/mm^3	<1	1
≥2000 to <4000/mm^3	4	19
≥4000/mm^3	2	33
unscored category	0	<1
Thrombocytopenia		
<50,000/mm^3	0	0
≥50,000 to <130,000/mm^3	1	8
≥130,000/mm^3	1	10
Anemia	0	6
Granulocytopenia	<1	2
Epistaxis	0	1
Skin and Appendages		
Dermatitis	8	23
Alopecia	3	22
Pruritus	1	2
Skin discoloration	0	2
Urticaria	<1	0
Body as a Whole		
Fatigue	6	11
Fever	3	5
Rigors	3	5
Chest pain	<1	1
Edema	1	1
Resistance Mechanisms		
Infection	5	12
Special Senses		
Taste Perversion	8	8
Altered sense of smell	1	1
Musculoskeletal System		
Arthralgia	5	4
Myalgia	3	2
Central and peripheral nervous system		
Dizziness	3	4
Headache	3	4
Paresthesia	2	3
Ataxia	0	2
Psychiatric		
Somnolence	3	2
Depression	1	2
Nervousness	1	2
Insomnia	1	1
Anxiety	1	1
Forgetfulness	0	1
Vision		
Abnormal tearing	0	4
Blurred vision	1	2
Conjunctivitis	<1	2
Liver and biliary system		
Hyperbilirubinemia	<1	1

In worldwide experience with ERGAMISOL, less frequent adverse experiences included exfoliative dermatitis, periorbital edema, vaginal bleeding, anaphylaxis, confusion, convulsions, hallucinations, impaired concentration, renal failure, elevated serum creatinine, and increased alkaline phosphatase. An encephalopathy - like syndrome has been reported in patients treated with ERGAMISOL.

The following additional adverse experiences have been reported for fluorouracil alone: esophagopharyngitis, pancytopenia, myocardial ischemia, angina, gastrointestinal ulceration and bleeding, anaphylaxis and generalized allergic reactions, acute cerebellar syndrome, nystagmus, dry skin, fissuring, photosensitivity, lacrimal duct stenosis, photophobia, euphoria, thrombophlebitis, and nail changes.

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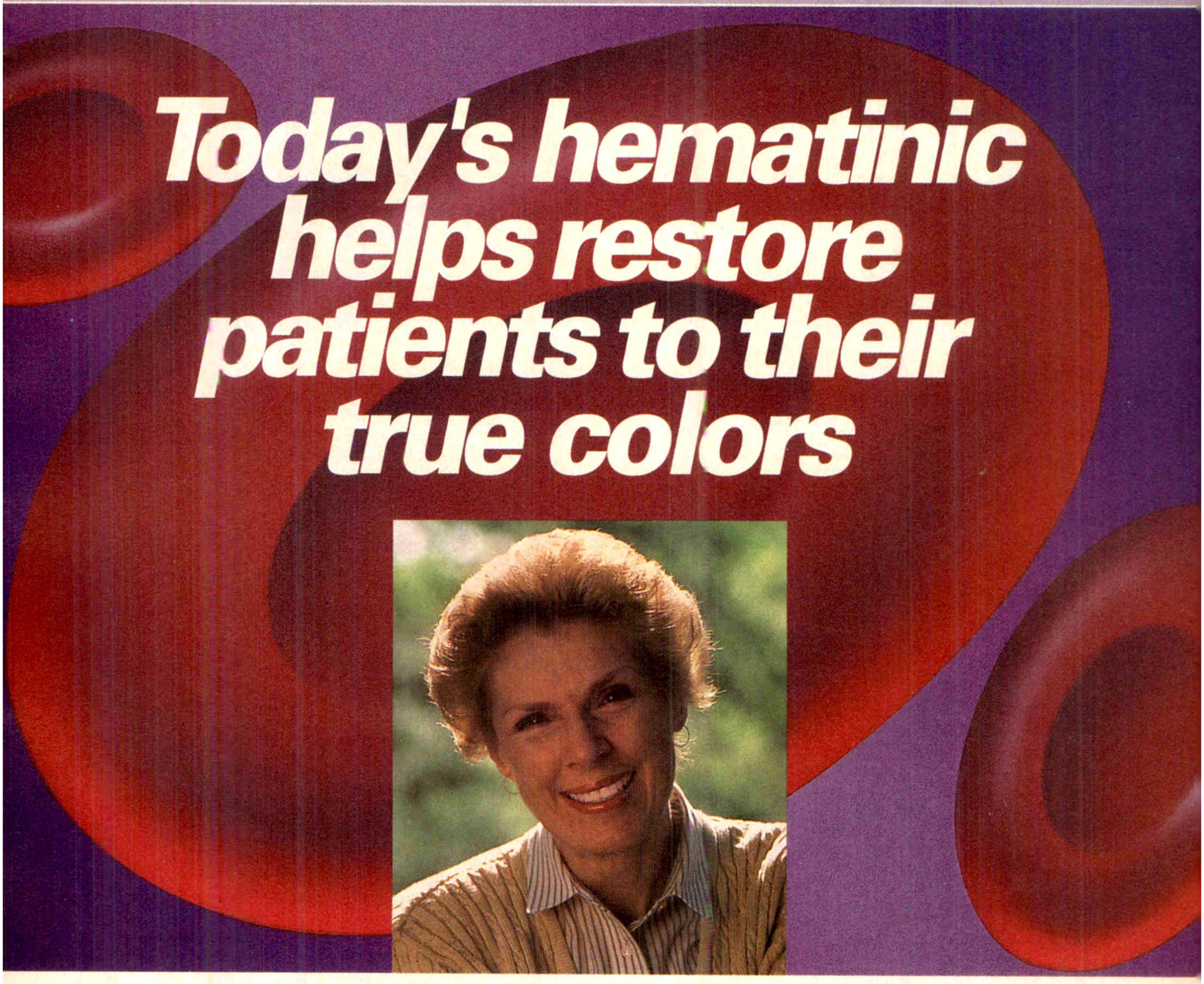
Today's hematinic helps restore patients to their true colors

Anemia is a growing problem — beyond hematologic parameters

The Elderly
☐ *Risk for anemia increases with chronic disease, concomitant medication, G.I. surgery*[1-3]

Surgical Patients
☐ *Use of autologous transfusions*[4] *may increase anemia*

Limited Heme Iron Consumption
☐ *May predispose patients to iron deficiency anemia,*[5] *and strict vegetarianism may help induce vitamin B_{12} deficiency*[6]

The complete hematinic, complete with intrinsic factor

TRINSICON's unique formulation provides the necessary nutrients for successful erythropoiesis
☐ *Vitamin B_{12} with Intrinsic Factor*
☐ *Iron* ☐ *Folic acid* ☐ *Other B-complex vitamins*
☐ *Vitamin C, which activates folic acid and increases iron absorption*

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☐ *Iron deficiency* ☐ *Vitamin B_{12} deficiency*
☐ *Folate deficiency*
(The specific cause[s] of the anemia should always be investigated.)

TRINSICON® **THE COMPLETE HEMATINIC**
Hematinic Concentrate with Intrinsic Factor

Please see Brief Summary of Prescribing Information on adjacent page.

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References: 1. Daly MP. Anemia in the elderly. *Am Fam Physician.* 1989;39(3):129-136. **2.** Clementz GL, Schade SG. The spectrum of vitamin B_{12} deficiency. *Am Fam Physician.* 1990;41(1):150-162. **3.** Stander PE. Anemia in the elderly: symptoms, causes, and therapies. *Postgrad Med.* 1989;85(2):85-96. **4.** Lampe GH. Blood loss and blood transfusions. *Acta Chir Scand Suppl.* 1988;550:88-94. **5.** Who really needs nutrition supplements? *Patient Care.* 1984;18(10):86-124. **6.** Robinson CH, Lawler MR. The water-soluble vitamins: the vitamin-B complex. In: *Normal and Therapeutic Nutrition.* 16th ed. New York, NY: Macmillan Publishing Co;1982:235.

Brief Summary
TRINSICON®
Hematinic Concentrate with Intrinsic Factor
A Highly Potent Oral Antianemia Preparation

INDICATIONS AND USAGE: TRINSICON® is a multifactor preparation effective in the treatment of anemias that respond to oral hematinics, including pernicious anemia and other megaloblastic anemias and also iron-deficiency anemia. Therapeutic quantities of hematopoietic factors that are known to be important are present in the recommended daily dose. **CONTRAINDICATIONS:** Hemochromatosis and hemosiderosis are contraindications to iron therapy. **PRECAUTIONS: General:** Anemia is a manifestation that requires appropriate investigation to determine its cause or causes. Folic acid *alone* is unwarranted in the treatment of pure vitamin B_{12} deficiency states, such as pernicious anemia. Folic acid may obscure pernicious anemia in that the blood picture may revert to normal while neurolological manifestations remain progressive. As with all preparations containing intrinsic factor, resistance may develop in some cases of pernicious anemia to the potentiation of absorption of physiologic doses of vitamin B_{12}. If resistance occurs, parenteral therapy or oral therapy with so-called massive doses of vitamin B_{12} may be necessary for adequate treatment of the patient. No single regimen fits all cases, and the status of the patient observed in follow-up is the final criterion for adequacy of therapy. Periodic clinical and laboratory studies are considered essential and are recommended. **Pregnancy: *Pregnancy Category C:*** Animal reproduction studies have not been conducted with TRINSICON® It is also not known whether TRINSICON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRINSICON should be given to a pregnant woman only if clearly needed. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRINSICON is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 10 have not been established. **ADVERSE REACTIONS:** Rarely, iron in therapeutic doses produces gastrointestinal reactions, such as diarrhea or constipation. Reducing the dose and administering it with meals will minimize these effects in the iron-sensitive patient. In extremely rare instances, skin rash suggesting allergy has been noted following the oral administration of liver-stomach material. Allergic sensitization has been reported following both oral and parenteral administration of folic acid. **OVERDOSAGE: Symptoms:** Those of iron intoxication, which may include pallor and cyanosis, vomiting, hematemesis, diarrhea, melena, shock, drowsiness, and coma. **Treatment:** For specific therapy, exchange transfusion and chelating agents. For general management, gastric and rectal lavage with sodium bicarbonate solution or milk, administration of intravenous fluids and electrolytes, and use of oxygen. **DOSAGE AND ADMINISTRATION:** One capsule twice a day. (Two capsules daily produce a standard response in the average uncomplicated case of pernicious anemia.)

Manufactured for
Russ Pharmaceuticals, Birmingham, AL 35242
by Central Pharmaceuticals, Seymour, IN 47274
June 1990

RUSS®
Russ Pharmaceuticals, Inc.

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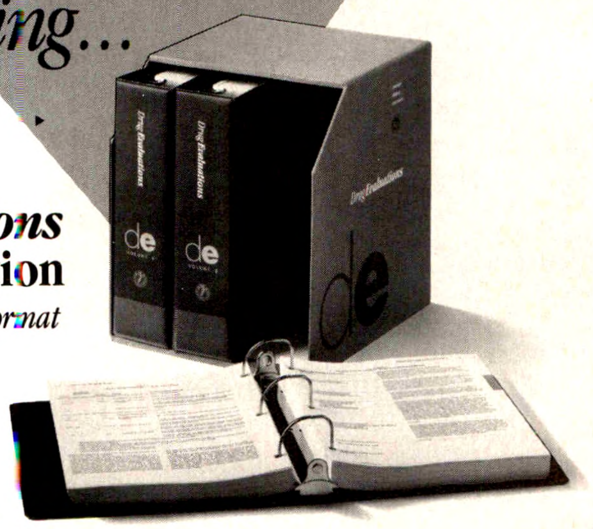

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Selection Factors Resulting in Improved Survival After Surgical Resection of Tumors Metastatic to the Lungs

Francesco M. Marincola, MD, James B. D. Mark, MD

• From 1973 through 1987, a total of 140 patients underwent 184 operations for removal of metastatic tumors to the lungs. The number of lesions removed ranged from one to 30. Of the patients, 44% had solitary lesions. Overall 3-year survival was 62.6%, and 5-year survival was 48.2%. In all primary tumors except melanoma and breast cancer, 3-year survival was greater than 50% and 5-year survival was greater than 40%. With rare exceptions, the operation of choice for unilateral lesions was ipsilateral thoracotomy, and for bilateral lesions it was median sternotomy. Adequate conservative resection was the rule. There were three pneumonectomies, 25 lobectomies, 71 single wedge resections, 38 multiple unilateral wedge resections, and 47 bilateral wedge resections. There were no postoperative hospital deaths. Cox covariate analysis demonstrated improved survival in patients whose largest lesion was less than 1.5 cm in diameter and with disease-free interval longer than 1 year, but survival was not related to number of lesions or age of patient. An aggressive surgical approach is justified in patients with most primary tumors and a limited number of lung metastases less than 1.5 cm in diameter. Resection of metastases from melanoma and breast cancer should be accomplished after other sites of metastatic disease have been ruled out by the most stringent criteria.

(*Arch Surg.* 1990;125:1387-1393)

Surgical resection of metastastic tumors to the lung is becoming an acceptable modality of treatment in selected cases, particularly in patients with no evidence of metastases elsewhere and whose general condition predicts tolerance of the planned operation. In the absence of a prospective, randomized trial of treatment for patients with metastatic tumor to the lungs, careful patient selection becomes increasingly important.

Five-year cure rates in the 25% to 40% range in selected groups of patients have been reported in a number of studies.[1,2] Surgical treatment of metastatic osteogenic sarcomas has a reported 5-year survival rate between 30% and 46%,[1,3-7] with a lesser survival rate for soft-tissue sarcomas (between 10% and 33%).[1,8] Nonseminomatous testicular carcinomas have been reported to have a 5-year survival of about 60%,[9] gynecologic tumors between 36% and 54%,[1,10] renal cell carcinomas 27% to 54%,[1,11] colon tumors 38% to 40%,[12,13] ear, nose, and throat tumors 12% to 44%,[14,15] and metastatic melanoma 11% to 25%.[1,16,17] Survival has been shown to correlate with the number of metastatic nodules,[2,6-8,11] doubling time of the metastatic lesions,[2,4,8] and the length of time from the treatment of the primary tumor to lung recurrence.[7,8] Finally, metastatic tumor size has been shown to be a predictor of survival for renal cell carcinoma.[11]

Many of these factors determining survival were analyzed arbitrarily by dividing patients into two groups by intersection of a variable in continuity and then comparing the two groups on the basis of this variable without taking into account the other covariates. In this series we analyzed retrospectively the Stanford (Calif) experience in treating patients with metastatic disease to the lungs and with no evidence of disease in other parts of the body. Patients were treated independently from the site of the primary tumor, and all the available data were compared with a multiple linear regression model.

PATIENTS AND METHODS

From March 1972 to December 1987, a total of 217 patients with metastatic disease to the lungs were referred to the Division of Thoracic Surgery of Stanford University Medical Center for evaluation and treatment. Of these, 27 patients had lymphoma. Of the remaining 190 patients, 140 were found to meet the criteria for resection. Criteria for resectability included (1) the preoperative belief that removal of all tumor would be possible and (2) the belief that the patient would be able to tolerate the operation planned. Relative selection criteria were as follows: (1) primary tumor under control, (2) no metastases elsewhere, and (3) no effective alternative method of treatment.

The patients' average age was 41.3 ± 1.7 years, the youngest being a 4-year-old child and the oldest an 80-year-old man.

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Read before the 61st Annual Meeting of the Pacific Coast Surgical Association, Laguna Niguel, Calif, February 21, 1990.

Reprint requests to Stanford Medical Center, Room S283, Stanford, CA 94305 (Dr Mark).

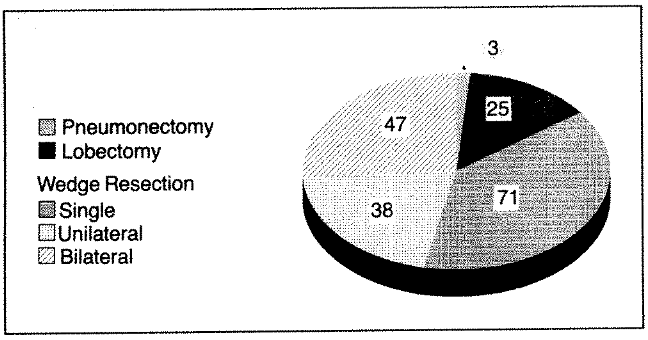

Fig 1.—Patient distribution according to the type of operation performed.

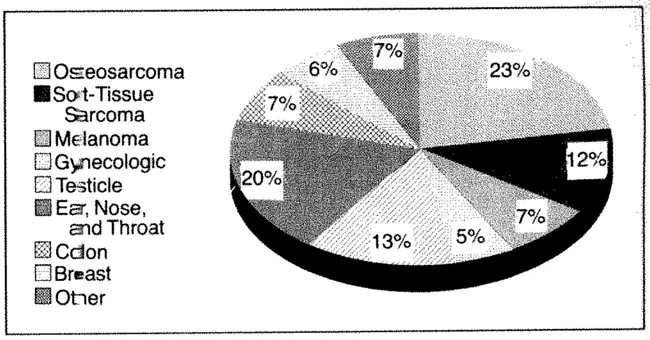

Fig 2.—Patient distribution according to the type of primary lesion.

Table 1.—Distribution of Patient Population by Primary Site*

Primary Site	% Sympomatic (No./Total)	No. of Nodules (Mean ± SEM)	% With Only 1 Nodule† (No./Total)	Size of Largest Lesion, cm
All	18.0 (25/140)	4.6 ± 0.5	43.6 (61/140)	2.1 ± 0.1
Osteosarcoma	12.5 (4/32)	5.1 ± 1.0	25.0 (8/32)	1.6 ± 0.2
Soft-tissue sarcoma	23.5 (4/17)	5.5 ± 1.6	35.2 (6/17)	2.7 ± 0.5
Colon	10.0 (1/10)	4.5 ± 2.6	70.0 (7/10)	3.6 ± 1.0
Kidney	42.9 (3/7)	3.6 ± 1.8	42.9 (3/7)	1.8 ± 0.3
Testicle	11.1 (2/18)	7.4 ± 2.4	44.4 (8/18)	2.1 ± 0.4
Breast	11.1 (1/9)	1.4 ± 0.2	55.6 (5/9)	2.1 ± 0.6
Melanoma	22.2 (2/9)	1.8 ± 0.8	88.9 (8/9)	2.4 ± 0.4
Ear, nose, and throat	16.0 (4/25)	4.9 ± 1.3	36.0 (9/25)	1.9 ± 0.3
Gynecologic	42.9 (3/7)	3.6 ± 1.2	28.6 (2/7)	3.4 ± 0.7
Bladder	25.0 (1/4)	1.0 ± 0.0	100.0 (4/4)	1.5 ± 0.5

*Two patients had primary sites other than those listed.
†At the time of the first thoracotomy.

When unilateral lesions were seen on a chest computed tomographic (CT) scan, the patient underwent lateral thoracotomy on that side with resection of the lesions by the most conservative resection that allowed complete removal of tumor with an adequate margin of normal tissue. If a lesion was peripheral in location, a limited thoracotomy incision was carried out. This did not allow complete evaluation of the remainder of the lung in many cases. Almost all patients with bilateral metastases underwent simultaneous resection of all lesions by a median sternotomy approach. A double-lumen endobronchial tube was used for all patients except children. Three patients underwent pneumonectomy, 25 single or multiple lobectomy, 71 single wedge resection, 38 multiple unilateral wedge resections, and 47 multiple bilateral wedge resections at one operation (Fig 1). There was one early postoperative death. A patient with metastatic testicular cancer died of tumor embolus to the pulmonary artery 10 days after his operation while sitting at his desk at work.

Of the 140 patients, 38 did not have a complete 5-year observation period; 17 patients returned to the referring institution and failed to keep their follow-up appointment with us. Thirteen patients are still under our care, but their operations were less than 5 years ago. Two patients moved to a distant area, and 6 patients suddenly became unavailable for follow-up after prolonged observation.

Data were recorded and analyzed by means of MEDLOG V89.1 (Information Analysis Corp, Mountain View, Calif). Unless stated otherwise, data are presented as means ± SEM. When indicated, parametric analysis was used with nonpaired-sample Student's *t* test to compare means between groups and analysis of variance to compare means among groups. Fisher's Exact Test and χ^2 test for equality of percentages were also used when appropriate. Multiple linear regression analysis[18] and Cox covariate-adjusted survival analysis[19] were used to analyze the effect of different covariates on one single variable or on survival. The survival rate was calculated from the time of the first thoracotomy. Survival curves were plotted according to the Kaplan-Meier table, and differences in survival between different groups were analyzed by the log-rank (Mantel-Haenszel) test for equality of survival care.[18]

RESULTS

Distribution of patient population according to the primary site of tumor is presented in detail in Table 1 and graphically in Fig 2. A large number of patients presented with sarcomas (either osteogenic or from soft tissue); the second largest group included patients presenting with epithelial tumors such as colon or breast carcinomas or tumors originating in the oropharynx and larynx, mostly squamous cell carcinomas (13/25, 52%) and adenocarcinomas (7/25, 28%).

Of the patients, 18.0% (25/139) presented with symptoms; however, the incidence of symptoms varied according with the type of primary tumor (Table 1, Fig 3).

One single area of pulmonary involvement at the time of each thoracotomy was present in 47.4% of the patients (Fig 4). This does not differ from the 43.6% (61/140) incidence of solitary pulmonary nodules when only the first thoracotomy was taken into account for each patient. If subsequent metastases not occurring at the site of previous resection are considered evidence of multiple foci of pulmonary involvement, then 34.3% patients (48/140) had only one metastatic lesion during the entire observation period. There was a statistically significant variation among groups in the number of patients presenting with only one lesion (analysis of variance, $P<.01$); however, the average number of pulmonary nodules according to the primary site did not differ significantly among groups ($P>.05$) (Table 1). Differences among groups were

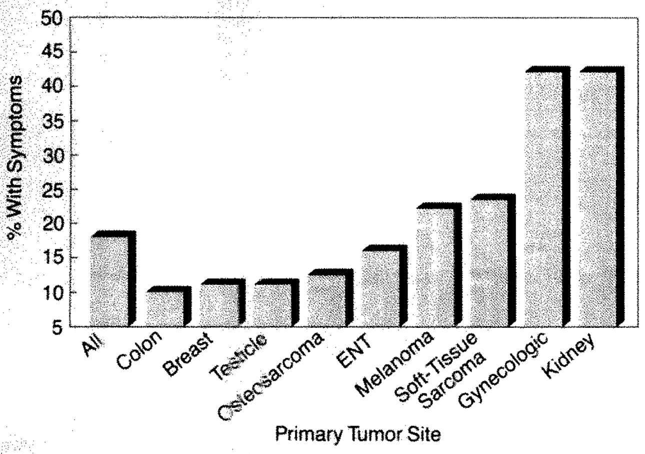

Fig 3.—Frequency of presentation with symptoms according to the primary tumor site. ENT indicates ear, nose, and throat.

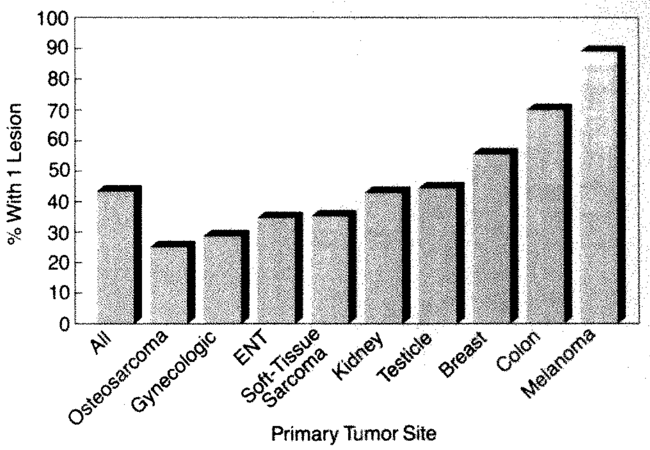

Fig 4.—Percentage of patients found to have a solitary nodule at the time of each thoracotomy. ENT indicates ear, nose, and throat.

Table 2.—Kaplan-Meier Survival Probabilities

Primary Site	N	Survival Probability, % (±SEM) 3-y	5-y	10-y
All	140	62.6±4.7	48.2±5.1	41.3±5.7
Osteosarcoma	32	60.0±9.9	46.1±10.4	39.5±10.8
Soft-tissue sarcoma	17	76.9±11.7	57.7±18.8	57.7±18.8
Colon	10	77.8±13.9	64.8±16.5	. . .
Kidney	7	80.0±17.9	53.3±24.8	. . .
Testicle	18	70.7±11.0	70.7±11.0	. . .
Breast	9	42.9±18.7	21.4±17.8	. . .
Melanoma	9	25.0±15.3	12.5±11.7	. . .
Ear, nose, and throat	25	53.5±11.5	41.6±11.6	. . .
Gynecologic	7	83.3±15.2	55.6±24.8	. . .
Bladder	4	33.3±27.2	. . .	. . .

remarkable for differences between melanomas and breast cancer (respectively, 1.8 ± 0.8 and 1.4 ± 0.2 lesions) vs testicular tumors (7.4 ± 2.4 lesions) ($P<.05$ in both cases).

The difference in size of the largest lesion found at thoracotomy was close to significance among groups (analysis of variance, $P=.06$) but not significant between different groups ($P>.05$ in all cases) (Table 1).

Table 2 gives 5-year survival for the individual groups. Overall 3-year survival was 62.6% ± 4.7 and 5-year survival was 48.2% ± 5.1, which is strongly in contrast with the 10.1% probability of survival at 5 years in our population of patients who were not operated on (36 patients). Survival was not particularly affected by the type of primary tumor except for breast cancer and melanoma, in which 5-year survival was 21.4% ± 17.8% and 12.5% ± 11.7%, respectively ($P<.001$) (Fig 5). Cox covariate analysis did not show a significant correlation between survival and patient age ($P=.67$), presence of symptoms at the time of diagnosis ($P=.45$), number of pulmonary nodules ($P=.89$), and amount of cigarettes previously smoked ($P=.51$). However, there was a strong statistical correlation between the size of the largest lesion (whether single or multiple) and survival ($P<.01$). There was also a statistically significant correlation between disease-free interval and survival ($P<.05$). These data are presented graphically in Figs 6 through 8. Figure 6 shows no difference in survival ($P>.05$) between patients presenting with one nod-

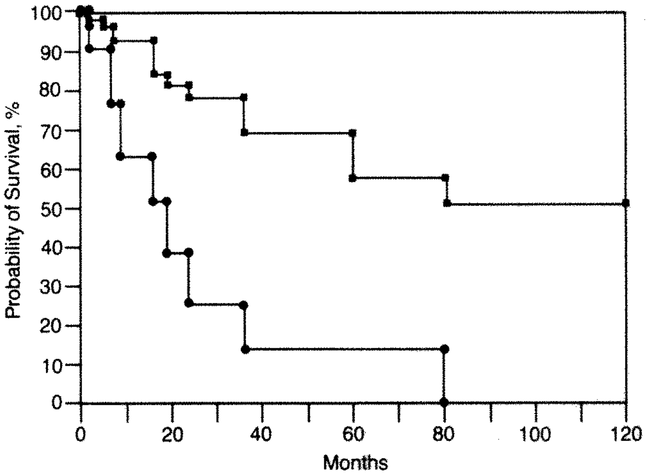

Fig 5.—Survival rate calculated according to the Kaplan-Meier table for patients with melanoma (circles) vs all other patients (squares). Difference in survival was analyzed by the log-rank (Mantel-Haenszel) test for equality of survival curve (Mantel-Haenszel $P<.001$).

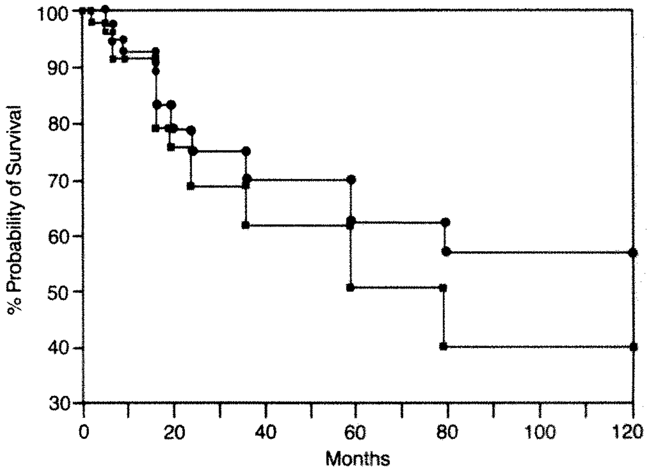

Fig 6.—Survival rate calculated according to the Kaplan-Meier table for patients presenting with one nodule (squares) and patients presenting with more than one nodule (circles). Difference in survival was analyzed by the log-rank (Mantel-Haenszel) test for equality of survival curve (Mantel-Haenszel $P>.05$).

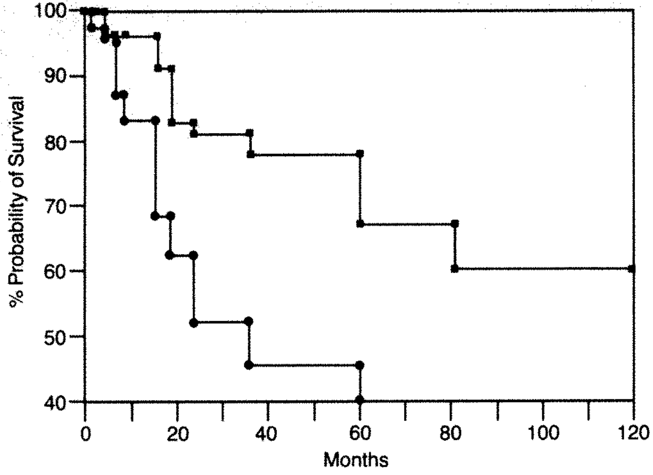

Fig 7.—Survival rate calculated according to the Kaplan-Meier table for patients with diameter of the largest lesion greater than (circles) or less than or equal to (squares) 1.5 cm (median distribution). Difference in survival was analyzed by the log-rank (Mantel-Haenszel) test for equality of survival curve (Mantel-Haenszel $P<.01$).

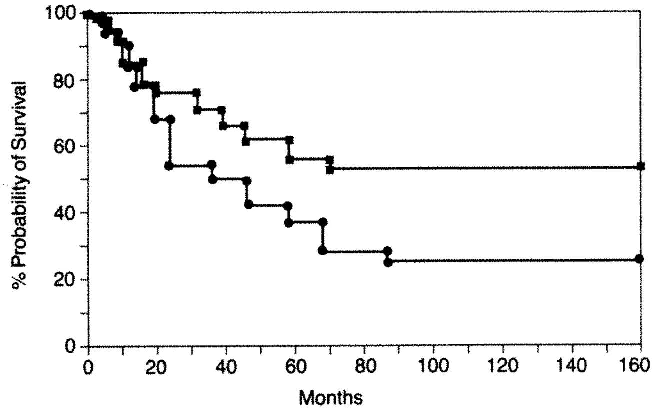

Fig 8.—Survival rate calculated according to the Kaplan-Meier table for patients with disease-free interval longer (squares) or shorter (circles) than 1 year. Difference in survival was analyzed by the log-rank (Mantel-Haenszel) test for equality of survival curve (Mantel-Haenszel $P=.08$).

ule and patients presenting with more than one nodule; the slightly worse survival of the single-nodule group might be attributed to the fact that this group included eight of the nine patients with melanoma, which has by far the worst prognosis; however, almost complete overlap is noted if these patients are removed from the calculation (data not shown). If patients without melanoma were divided arbitrarily into two groups, one group including the patients presenting with four or fewer metastases (100 patients) and the other including patients presenting with more than four metastases (31 patients), a difference in 5-year survival was noted (55% vs 39%); however, this was not significant ($P=.24$).

Figure 7 shows the difference in survival between two groups of patients divided empirically by the diameter of their largest lesion (whether single or multiple) with 1.5 cm, which represents the median in the distribution of tumor diameters among all the patients, chosen as the cutoff point. A significant difference in survival was noted between these two groups ($P<.01$). The median disease-free interval was 652 days. When patients were divided according to the median disease-free interval, no significant difference was noted in survival curves among the two groups ($P=.15$). The difference in survival is closer to significance if patients are divided between those who developed metastatic disease during the first year from the treatment of their primary tumor and those whose metastatic spread was evident after 1 year ($P=.08$) (Fig 8).

Of the 18 patients with nonseminomatous testicular carcinoma, all received chemotherapy before thoracotomy. Ten of them were found to have benign lesions at thoracotomy (either scar tissue or mature teratoma), and 8 were found to have malignant tissue (histologic features similar to those of the primary tumor). The 5-year survival was better for the patient group found to have benign lesions (87.5% vs 62.5%); however, this did not differ statistically, probably due to the small sample size ($P=.19$).

Male patients ($n=92$) had a better 5-year survival than did female patients ($n=48$) (54.1% vs 36.7%). The difference, however, was not statistically significant ($P=.10$). This difference in survival according to patient sex was noted also when a more homogeneous population of patients was analyzed, such as patients with sarcomas, in which case male patients ($n=33$) had a better 5-year survival (52.0%) than did female patients ($n=16$; 5-year survival, 21.0%; $P>.05$).

COMMENT

Surgical treatment of metastatic tumors to the lungs has become an important part of the treatment of cancer patients. In the absence of randomized, prospective clinical trials, the selection of patients for surgical treatment becomes increasingly important.

With few exceptions, surgical resection of metastatic tumor deposits in the lungs should be carried out with curative intent. Exceptions to this rule include operations for staging of certain cancers, particularly testicular tumors, and palliation of specific symptoms. "Debulking" of metastatic tumors to the lung to make other treatment more effective is a highly questionable concept. The use of modern diagnostic methods, especially CT, should result in relatively few instances of inability to resect tumor thought preoperatively to be removable. There will certainly be cases of miliary spread of tumor to the visceral or parietal pleura not detected before thoracotomy, but these will be infrequent in patients otherwise thought to be potentially curable. It should be rare indeed to find a lesion unresectable because of size or location not realized preoperatively.

In our series we report survival rates for each tumor type that are similar to or slightly better than those previously reported in other series. We attribute this improved survival to two factors: strict selection of patients undergoing thoracotomy and an improvement in multimodality therapies, since many of our patients received a combination of aggressive chemotherapeutic or radiotherapeutic treatments for their disease. The impact of modern chemotherapy or radiotherapy on the improved survival of these patients is difficult to quantitate but cannot be minimized.

The quality of our analysis is difficult to assess because this is a retrospective study. In survival analysis, censoring is probably the most important limiting factor. Of the 140 patients, 38 did not have a complete 5-year observation period since their first thoracic operation for metastatic cancer. Of this number, 17 patients were unavailable for follow-up immediately after their surgical procedure because they returned to the referring institution and failed to keep their follow-up appointment (immediate censoring). Thirteen patients are still under our care, but their operations were less than 5 years ago (right censoring). Two patients were unavailable for follow-up because they moved to a distant area, at which time they were both without evidence of disease (pure random censoring). Finally, six patients were suddenly unavailable for follow-up after prolonged observation, suggesting death as the cause of censoring. Since immediate, right, and pure random censoring do not affect the quality of survival analysis (except by decreasing sample size), we calculate that the bias in our statistics due to censoring should not exceed 4%.

Survival has been shown to be worse if multiple metastatic nodules are present when the primary tumor is an osteogenic sarcoma,[6,7] soft-tissue sarcoma,[2,8] or nonseminomatous testicular tumor.[2,11] There is, however, no correlation between nodule number and prognosis when the primary tumor is a carcinoma.[11,12] In our series, we were unable to find a correlation between survival and the number of metastatic lesions at presentation. This might be due to the heterogenous population of patients, most of whom had a carcinoma as the primary tumor. Furthermore, patients with testicular tumors, who had the best 5-year survival rates, were also the one presenting with the highest average number of lesions (seven), whereas patients with melanoma and breast cancer, which have the worst prognosis, tended to present with only one lesion.

Metastatic tumor size has been shown previously to be a predictor of survival for renal cell carcinoma.[11] In our series, the size of the largest metastasis was the most significant predictor of survival both by multivariate analysis and by arbitrarily splitting patients according to the median of the largest diameter. The other predicting variable found to be of significance by multivariate analysis was the disease-free interval. The usefulness of these findings is unknown. Certainly we do not believe that patients should be denied operations on the basis of the size of their metastasis or disease-free interval; on the other hand, these factors may help in decision making in borderline situations in which other clinical factors may favor or contraindicate an operation.

We are currently using the following criteria for selection of patients for pulmonary metastectomy.

1. On the basis of preoperative studies, especially CT of the chest, it is the surgeon's judgment that all tumor can be removed. Single or multiple wedge resection will in most cases be adequate. More extensive resection is necessary only if the size or location of the tumor will not allow safe or complete wedge resection or, as is the case occasionally, when it is important to remove involved hilar nodes in continuity with the metastatic tumor. As noted previously, when a unilateral lesion or lesions are seen on CT, ipsilateral thoracotomy is performed. This might be controversial when the primary lesion is a soft-tissue sarcoma or other primary tumor frequently presenting with multiple lesions. Roth and coworkers[20] compared the results of patients with soft-tissue sarcomas preoperatively thought to have unilateral lesions who underwent median sternotomy vs unilateral thoracotomy. Interestingly, 45% of their patients who were thought preoperatively to have unilateral disease by CT scan were found at the time of the median sternotomy to have bilateral lesions. A single peripheral lesion may be removed by means of a limited incision, whereas multiple unilateral lesions may require wider exposure. A median sternotomy approach is used for most bilateral lesions. If the lesions are large or proximally located, staged unilateral thoracotomies may be indicated. If the lesions are posteriorly placed in the left lower lobe, left thoracotomy should generally be planned. Rotation of the heart, necessary to expose this area from the anterior approach, may result in hypotension and arrhythmias. Lesions peripherally located in all other lobes may generally be removed by a median sternotomy incision, and all lobectomies and pneumonectomies except for left lower lobectomy can be done by this approach as well.

2. The patient should be able to tolerate the operation that is planned. The mortality and morbidity of operations to remove metastatic tumors to the lungs should be very low. We have had no in-hospital mortality, and morbidity has been minimal.

3. The primary tumor should be under control. This is a good concept, but the definition usually needs amplification. The concept of control is sometimes uncertain, and certainly the length of time that the primary tumor has been under control may be influential. It may be more accurate to say that the primary tumor is not known *not* to be under control.

4. There should be no tumor elsewhere. On occasion, for instance in testicular tumors, there may be retroperitoneal nodes involved at the time pulmonary metastases are removed. Both of these metastatic areas may be treated simultaneously or at different times. An appropriate evaluation should be done in each instance before thoracotomy. The amount of investigation, however, might vary according to the primary tumor. Sarcomas, for example, tend to metastasize directly to the lung; therefore, a thorough evaluation of the primary site by physical examination and bone scan and a CT scan of the chest are probably all that is needed in preoperative evaluation. Carcinomas, on the other hand, may metastasize to different places at the same time, and therefore a more comprehensive evaluation should be obtained that includes the liver. Particularly extensive evaluation should be carried out in patients with melanoma, in which the likelihood of disease somewhere else is high and the benefits from the thoracotomy minimal. In these patients, a CT scan of the head should also be obtained before subjecting the patient to a thoracotomy.

5. There should be no other reasonable treatment available. As new chemotherapeutic agents become available, some may be found that will be curative for metastatic tumors. At the present state of our knowledge, most chemotherapy is palliative and does not replace surgical resection of metastatic tumors to the lungs.

6. Special consideration should be given to melanoma metastases. Wong et al[17] reported a 31% survival rate in highly selected patients with melanoma who had normal brain, lung, and abdominal CT scans and a calculated tumor doubling time of greater than 40 days. Our experience is more limited, and our criteria for operation are perhaps less strict; this may account for the poorer results in our patients. It is interesting to note that eight of nine patients had solitary lesions, and still this did not contribute toward better survival. Perhaps the number of lesions is not as critical as the other factors described, and extremely stringent criteria should be applied in patients with melanoma before offering them the option of surgical excision of their metastatic disease.

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Discussion

KENNETH P. RAMMING, MD, Los Angeles, Calif: The 50% three-year cure rate in a multiplicity of tumors with a surgical mortality of zero in 140 patients demonstrates that surgery for pulmonary metastases is safe, first-line treatment in patients amenable to surgery, and all other treatment is adjunctive. The excellent results reflect a judicious selection of the appropriate patients for pulmonary resection. That the disease-free interval of greater than 1 year is a significant prognostic factor, and that patients with smaller lesions have a more favorable outcome, is consistent with experience at UCLA. That survival is not related to the number of lesions is also consistent with our experience. We have found that patients with sarcomas more often have indications for pulmonary resection than do patients with other epithelial tumors. Patients with melanoma rarely benefit from resection of pulmonary metastases.

In malignant tumors for which effective combinations of systemic agents exist, the ideal treatment of pulmonary metastases is the institution of a trial of chemotherapy. If there is favorable slowing of the doubling time, or even regression of the pulmonary metastasis on serial chest roentgenograms (a negative doubling time), such a patient becomes an ideal candidate for surgical excision. After total excision of all gross tumor in the lungs, we treat vigorously postoperatively, in an attempt to control any disseminated micrometastatic, clinically inapparent, residual tumor cells that may be present in the body. Excellent chemotherapy is available in patients with germ cell tumors, and aggressive surgical resection is indicated in these patients. Chemotherapeutic agents such as high-dose methotrexate and cisplatin in combination with doxorubicin given preoperatively in patients with metastatic osteosarcoma results in a high response rate with a significant recurrence-free survival in over half of the patients. Although chemotherapy for soft-tissue sarcomas is not as effective as that for osteosarcoma, in patients who are properly selected, survival after resection for soft-tissue sarcoma should be between 30% and 35%. Further studies are necessary to evaluate the impact of new agents such as ifosfamide on these soft-tissue sarcomas.

There is no role for debulking of tumors to make some other treatment more effective. This may be possible in ovarian cancer, but it is not advisable for any of the tumors that the thoracic surgeon is likely to encounter. Even with so-called neoadjuvant therapy, subtotally resecting tumors in the chest is never indicated.

The approach to patients with pulmonary metastatic disease requires multidisciplinary input of medical oncologists who are familiar with solid tumor oncology as well as thoracic surgeons who are knowledgeable in chemotherapy and the effects of chemotherapy in tissues within the thorax, such as desmoplastic reaction encasing the pulmonary arteries and pleural surfaces, may be induced by pretreatment with chemotherapy. Such issues as pulmonary toxic effects and the timing of surgery after chemotherapy and radiation therapy are very important considerations in the treatment of these patients.

Ten patients a year is somewhat low. Should we recommend surgery in patients who have less favorable risk factors than those presented here, particularly those whose disease-free interval is much shorter than 1 year? Is the doubling time criteria used, and what is the shortest disease-free interval the authors will accept?

THEODORE X. O'CONNELL, MD, Los Angeles, Calif: The patients who were excluded are as important as the patients who were included in this study. The authors have told us that size is the primary criterion for selection. If this is the most important factor, then perhaps our medical colleagues should do chest roentgenograms and CT scans more frequently to pick up these tumors that are less than 1.5 cm. Or is size only a reflection of the inherent malignancy of the tumor and of doubling time? There is no mention of the use of doubling time as a selection of patients, whereas most of the other articles in the literature have used this technique.

If roentgenograms are obtained every 6 or 12 months, slow-growing tumors will be much more likely to be under 1.5 cm and rapid-growing tumors greater than 1.5 cm. Is the size criterion really a doubling time and a rapidity of growth criterion?

JAMES E. GOODNIGHT, JR, MD, Sacramento, Calif: In most series of patients undergoing resection for pulmonary metastases, the surgeon will find at operation one-third more nodules than are seen on preoperative imaging studies, and there are instances of unexpected bilaterality of the tumors. How many times did the authors find more nodules at surgery than on preoperative studies, suggesting that perhaps median sternotomy and examination of both lungs should be the standard approach to this problem?

DAVID TAPPER, MD, Seattle, Wash: What happened to the survival data on the osteogenic group? What about the testicular group? The authors mentioned that a large percentage of the lesions that they removed were, in fact, benign. Was this true in any of the other categories? Were a large percentage benign, and if so, did they represent changes in biologic characteristics? Is the wedge resection extensive enough? What percentage of the patients had recurrences in the previous incision?

In the large Stanford group, is there a comparable group that the oncologists have looked at? In our own Wilms' tumor study we also favor resection of solitary metastases. However, in a retrospective review by the oncologists in the National Wilms' tumor study, they found a group similar to the surgical group. Have the authors' oncologists identified a similar group? Would they be willing to study in a prospective fashion using some of the information that they have identified and randomize a group of individuals into either category? Would they be willing to treat some with multimodal chemotherapy and some with surgery?

DONALD E. WAGNER, MD, Santa Monica, Calif: Was the thoracotomy at this point in the patient's disease responsible for the increase in survival rate, or were there other factors after the thoracotomy, such as radiation therapy and chemotherapy? A 1.5-cm tumor in the lung is very small.

RICHARD G. FOSBURG, MD, La Jolla, Calif: This report provides validity to the observations that the smaller lesion and the longer disease-free interval are important determinants of outcome. One third of the patients referred as candidates were excluded. The authors have not identified the basis for elimination. I find this as important as those who were subjected to the procedure.

Have the authors learned any subtleties that can tell us why patients are not good candidates? I have always waited at least 3 months before subjecting patients to resection for metastatic lung nodules to document freedom from additional new nodules. The authors leave unstated the number of patients who died of their tumors, and, more importantly, they do not tell us whether the deaths were due to the primary or metastatic sites. I am curious as to whether they tabulated those who subsequently demonstrated additional lung metastases and the reasons why the additional resections were not undertaken.

All patients subjected to a resection were judged to be free of disease elsewhere. Can we learn anything by analyzing the sites of their subsequent demonstration? Would a delay in resection have permitted the recognition?

Eighteen percent of their patients were identified as presenting with symptoms, but we were not told their nature. Is there any message associated with symptoms, since the patients were presumed to have met the criteria that the primary tumor was under control and that there was no evidence of disease elsewhere?

Why is there such a failure with solitary nodules when they are melanoma, breast, or bladder secondaries? Are we prematurely subjecting these patients to resection? Are we coming too close to identifying a number that we should regard as a deterrent to resection? I suggest to the authors that maybe another report lies in the analysis of their failure rather than representing their successes.

ORLO H. CLARK, MD, San Francisco, Calif: I would recommend that patients with pulmonary metastases from endocrine tumors should be strongly considered for removal of these tumors. These patients often live for years with metastatic disease and often die of metabolic disease rather than of the tumor. Our group has treated pulmonary metastases due to medullary thyroid cancer, follicular thyroid cancer, parathyroid cancer, and other metastatic endocrine tumors, and most of these patients have done very well.

JOHN R. BENFIELD, MD, Sacramento, Calif: Magnetic resonance imaging and CT scanning are an imperfect art. In our experience with operation in patients with lymphomas (*Ann Thoracic Surg*. 1987;44:363-369), fully 38% of the patients who were thought to have lesions likely to be lymphomas turned out to have other diseases or not to have cancer at all. Patients with a preoperative diagnosis of metastatic lung cancer who are proved by operation not to have lung cancer are provided an important service by the operation. If preoperative chemotherapy is to be given, it is important to be absolutely certain that these patients have metastases; one should not rely on a history of cancer and positive CT or magnetic resonance findings.

How far should one push operation in the management of metastases? What is the limit? How many thoracotomies should be done for such patients? Our general policy is that one operation for presumed or proved metastasis is perfectly appropriate; a second operation is sometimes indicated. In my opinion, a third operation to resect metastases is rarely, if ever, indicated.

I consider segmentectomy the operation of choice for the treatment of metastases when wedge resection is not adequate. Why did the authors use segmentectomy to accomplish resections in any of their patients?

DR MARK: There may be other reasons besides therapeutic resection to do thoracotomies in patients with metastatic tumors to the lungs. One may be for analysis of estrogen or other receptors. There may be development of monoclonal antibodies for growing tumors to test them against certain chemotherapeutic agents, but the main reason for operation in these patients is with curative intent.

Dr Fosburg, we operate on any patients who we think can stand to be operated on and in whom we think we can resect all the lesions, even if we operate on them two, three, or four times. We have operated as many as five times, and others have operated many more times than that if there are no alternative forms of treatment. We have one patient with renal cell metastases on whom we have operated five times.

The concept of temporizing after seeing the lesion the first time and waiting for something to happen has never appealed to me very much. If you have a melanoma or something that is rapidly growing or an exceptionally short disease-free interval, it may be advisable. We have had patients who presented with their primary tumor and their lung metastasis at the same time. The referring surgeon has operated on the primary tumor, and once the patient has recovered, say in a few weeks, we have operated on the lung metastasis. It is better to say we know the primary tumor is *not* under control. We would not do that if we knew there was recurrent primary tumor.

The deaths in these patients were usually due to metastases elsewhere or lack of control of the primary tumor, not of recurrence of the lung lesions. The symptoms were pain, obstructive symptoms, and hemoptysis. We had few endocrine tumors. A couple of the thyroid tumors have had endobronchial and endotracheal metastases. They were not included in this study. Things such as size of the tumor, number of lesions, and disease-free interval, which can be quantitated, were more apt to be reasons for operating on patients.

Dr Benfield, if you have a patient with melanoma and a solitary lung lesion, that is most likely to be melanoma. If you have a patient with a breast cancer and a solitary lung lesion, that is more likely to be a primary lung cancer. Breast cancer is not apt to be a solitary lesion.

We do segmentectomy and include that in the lesser resections, but not often. We do not hesitate to use it, but we believe that an adequate wedge resection is satisfactory when it can be carried out. Only two patients have had recurrences in the area of the wedge resection. Another more than 40 patients have had recurrences in other areas. Overall, 34% of the patients had lesions that were single, metastatic lesions to the lung.

Dr Thomas, it is true in testicular carcinoma that a number of the lesions are benign, either scar tissue or benign tumor. Ten patients had benign tumors or scar tissue, and eight had residual testicular carcinoma. The cure rates in those were 87% for the benign lesions and 62% for the ones with the residual tumor. These differences were not statistically significant because of the small numbers.

Another indication for operation in the testicular tumors is for staging. If there is residual cancer, the patient gets more chemotherapy. If there is not residual cancer, he or she does not.

Unexpected bilaterality was quite rare, but it certainly does happen. It is not expected to have more lesions than are seen on the CT scan. This is usually in lesions that are already bilateral, and that we are doing median sternotomy to take care of.

Dr Tapper, to our knowledge the oncologists are not following up these patients without operation. It would be nice if we had the courage to do a randomized, prospective study on patients with metastatic lesions to the lung and operate on some and not operate on others. I am afraid that it is not going to happen any time soon.

Heterotopic Tissue in Lymph Nodes

An Unrecognized Problem

Mark P. Sawicki, MD; Thomas J. Howard, MD; Edward Passaro, Jr, MD

• Heterotopic tissue in lymph nodes is both unknown to clinicians and a potential source of confusion with metastatic disease. We reviewed the English literature and found 289 cases of heterotopic tissue in lymph nodes. The majority (84%) of these patients were operated on for malignant neoplasms. The most frequent sites of occurrence was the pelvis (67%), followed by the axilla (14%), neck (14%), groin (3%), abdomen (2%), and mediastinum (less than 1%). The tissue seen is site-specific and frequently resembles a neighboring organ. Three cases have been reported in which heterotopic tissue was mistaken for metastatic disease. These cases illustrate the importance of being familiar with heterotopic tissue in lymph nodes and identifying it when it does occur, to avoid inappropriate therapy.

(*Arch Surg.* 1990;125:1394-1399)

It is not well known that heterotopic tissue may occur in lymph nodes. To our knowledge, there are no thorough reviews in the literature and its occurrence is only briefly mentioned in pathology textbooks.[1,2] This heterotopic tissue consists of aggregates of benign-appearing cells arising ectopically in lymph nodes. Because this tissue frequently resembles a neighboring organ, it may be misdiagnosed as metastatic disease.

Heterotopic tissue has been reported to occur in lymph nodes in the pelvis,[3,4] groin,[5,6] abdomen,[7,8] mediastinum,[9] axilla,[10,11] and neck.[12] A wide variety of tissues have been found, such as müllerian,[3] breast,[10] pancreas,[8] nevus,[11] and thyroid.[12] It is distinguishable from metastatic disease by its benign morphological characteristics. The histological appearance varies from cystic, glandular, or tubular structures to clusters of cells arranged in nests or cords. The tissue generally occupies a small portion of the lymph node and is usually clinically silent.

Due to the variation in the histologic appearance of heterotopic tissue in lymph nodes, many synonyms were used to describe this tissue. They have been referred to as choristomas,[13] benign glandular inclusions,[7] heterotopic tissue,[8] nonneoplastic tissue,[3] benign epithelial inclusions,[14] and aberrant tissue.[15] We prefer the designation *heterotopic tissue in lymph nodes*, because it encompasses various histologic types of tissue.

The purposes of this study were to review the English literature to (1) make the clinician more aware of heterotopic tissue in lymph nodes and their clinical importance; (2) identify which lymph node groups have been reported to contain heterotopic tissue; (3) identify the types of tissue involved; and (4) determine the frequency of occurrence at the different node groups.

METHODS

Using the National Library of Medicine database, the English literature from 1897 to 1989 was reviewed. We excluded almost all cases of so-called lateral aberrant thyroid. Prior to 1948, this term referred to normal or pathologic thyroid tissue located lateral to the internal jugular veins.[16] This thyroid tissue was often located in lymph nodes. Several reports stated that benign-appearing thyroid follicles in cervical lymph nodes could represent metastatic carcinoma from an occult thyroid primary site.[17-19] For thyroid follicles in cervical lymph nodes to be considered benign, a coexisting thyroid carcinoma must be excluded. This can be accomplished by performing subserial sections of the entire thyroid gland at sufficiently small intervals to exclude a neoplasm. Therefore, the only cases of heterotopic thyroid tissue included in this review are those in which the entire thyroid gland was subserially sectioned at 5-μm intervals.

RESULTS

A total of 289 cases were reviewed. The data are presented by tissue type in Table 1.

Pelvis

The majority of reports on heterotopic tissue have been in pelvic lymph nodes from lymphadenectomies for gynecologic disease. There were 20 such reports with 194 patients reported.[3,4,20-37] The ages ranged from 12 to 77 years (mean, 40 years [n = 30]). One hundred sixty-five (89%) of 186 patients were operated on for malignant disease (Table 2). The heterotopic tissue did not affect their prognosis.[20] Twenty-one (11%) of 186 patients had benign disease; however, no follow-up data are available.

The incidence of heterotopic müllerian tissue in pelvic lymph nodes varies from 2% to 34%.[20-35] The highest incidence

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Table 1.—Heterotopic Tissue in Lymph Nodes

Tissue	No. of Patients	Location	Reference No.
Müllerian	194	Pelvis	3, 4, 20-37
Pancreas	4	Celiac axis	8, 13, 39, 40
Colon	1	Mesenteric	41
Angiomyolipoma	1	Para-aortic	9
Thyroid	6	Cervical	12, 43
Parotid	29	Periparotid	15, 47
Nevus	4	Cervical	5, 11, 48, 49
	33	Axilla	5, 11, 49, 53
	9	Groin	5, 38
Breast	6	Axilla	10, 50-52
Unclassified	1	Groin	6
	1	Renal vessels	7
	1	Mediastinum	8
	1	Axilla	6

Table 2.—Heterotopic Tissue (Müllerian) in Pelvic Lymph Nodes

Primary Disease	No. of Patients	Reference No.
Malignant		
Cervical cancer	135	4, 20, 22, 27, 31, 32, 34, 35, 37
Uterine cancer	11	4, 22, 25, 26, 28, 31, 32, 34
Ovarian cancer	7	21, 22, 31, 34, 35
Vaginal cancer	2	4, 35
Urethral cancer	1	25
Anal cancer	2	4
Bladder cancer	1	36
Rectal cancer	1	35
Not specified	5	29
Benign		
Ovarian adenoma	2	34
Uterine leiomyoma	2	23, 32
Endometriosis	3	31, 32
Endosalpingiosis	1	30
Infection	1	24
Not specified	12	3
Autopsy	8	4, 28

Table 3.—Heterotopic Tissue in Inguinal Lymph Nodes

Primary Disease	No. of Patients	Tissue	Reference No.
Leiomyosarcoma	1	Nevus	5
Liposarcoma	1	Nevus	5
Melanoma	6	Nevus	5, 38
	1	Unclassified	6

Table 4.—Heterotopic Tissue in Abdominal Lymph Nodes

Primary Disease	No. of Patients	Tissue	Reference No.
Malignant			
Gastric cancer	2	Pancreas	8, 39
Colon cancer	1	Colon	41
Ileal cancer	1	Unclassified	7
Benign			
Cholecystitis	1	Pancreas	13
Kidney angiomyolipoma	1	Angiomyolipoma	9
Autopsy	1	Pancreas	40

(34%) was reported in women operated on for cervical carcinoma.[20] Remarkably, there have not been any reports of heterotopic tissue in the pelvic lymph nodes of men. One autopsy study reported that seven (14%) of 50 female and no male autopsy specimens contained heterotopic tissue.[4]

The distribution within the pelvis in one series was as follows: iliac, 13%; hypogastric, 52%; and obturator, 35%.[20] The majority were occult, but occasionally they enlarged the lymph node sufficiently to make it abnormal.[24] Usually one or two lymph nodes were involved, but as many as three or more were noted.[35]

Although the histologic appearance varied, some common features emerged.[3,4,20-37] The tissue resembled the epithelium lining the female genital tract (müllerian). Heterotopic tissue was reported in pelvic lymph nodes of women with malignant neoplasms and benign disease; the appearance of the heterotopic tissue was the same in both instances.[4]

Coexistent heterotopic tissue and metastases were seen in 10 patients.[4,23,34,35] In contrast to the metastases, the heterotopic tissue appeared remarkably benign. This was particularly evident in three patients in whom the metastatic tumor was of squamous cell origin while the heterotopic tissue had a glandular appearance.[34,35]

Carcinoma arising in heterotopic tissue is very rare. There is one report of an adenocanthoma arising in an endometriotic cyst in an obturator lymph node. The patient underwent radical hysterectomy and pelvic node dissection for a superficially invasive adenocarcinoma of the endometrium.[26]

Groin

There were nine cases of inguinal lymph nodes. The ages ranged from 8 to 61 years (mean, 38 years). Five (55%) of nine were male, and all were operated on for malignant neoplasms (Table 3). Coexistent heterotopic tissue and metastatic disease was not reported. There were eight instances of benign nevus cells in inguinal lymph nodes.[5,38] Heterotopic tissue, which was unclassifiable, was found in an inguinal lymph node of a 52-year-old woman who underwent bilateral groin dissections for malignant melanoma.[6]

Abdomen

Seven patients had abdominal lymph node involvement (Table 4); four were operated on for malignant neoplasms. There were no reports of coexisting metastatic disease and heterotopic tissue. Two of the patients were operated on for benign disease; however, no follow-up data were available.

Heterotopic pancreatic tissue was reported in four cases (B. S. Bhagavan, MD, unpublished data, 1990).[8,13,39] Pancreatic tissue was found in four lymph nodes around the common hepatic artery during a subtotal gastrectomy for adenocarcinoma of the stomach.[39] The pancreatic tissue was composed of glandular acini, ducts, and islets of Langerhans. Cystic glands and a 0.2-cm nodule of normal-appearing pancreatic tissue were embedded in a celiac lymph node in a 50-year-old woman undergoing cholecystectomy.[13] Heterotopic pancreat-

Table 5.—Heterotopic Tissue in Cervical Lymph Nodes

Primary Disease	No. of Patients	Tissue	Reference No.
Malignant			
Laryngeal cancer	1	Nevus	48
Melanoma	2	Nevus	5, 11
	1	Parotid	15
Benign			
Neck mass	3	Parotid	15
	1	Thyroid	43
Epidermoid cyst	1	Nevus	49
Acquired immunodeficiency syndrome	6	Parotid	47
Autopsy	5	Thyroid	12
	19	Parotid	15

Table 6.—Heterotopic Tissue in Axillary Lymph Nodes

Primary Disease	No. of Patients	Tissue	Reference No.
Malignant			
Breast cancer	16	Nevus	5, 11, 49, 53
	1	Breast	51
	1	Unclassifiable	6
Melanoma	13	Nevus	5, 11, 49
Basal cell cancer	1	Nevus	49
Benign			
Fibrocystic disease	2	Breast	10, 50
	1	Nevus	49
Fibroadenoma	1	Breast	51
Nevus	1	Nevus	5
Axillary mass	1	Breast	52
	1	Nevus	5

ic tissue was found in a celiac lymph node of a 44-year-old woman undergoing gastrectomy for adenocarcinoma of the stomach.[8] Heterotopic islets were seen in the peripancreatic lymph nodes of a 56-year-old man who died of end-stage liver disease (B. S. Bhagavan, MD, unpublished data, 1990). At autopsy, one peripancreatic lymph node was found to contain a nest of islet cells that stained positive for insulin, glucagon, and pancreatic polypeptide, and negative for gastrin and somatostatin. Acini and ducts were absent. Serial sectioning of the pancreas did not reveal a pancreatic neoplasm.

Unclassifiable heterotopic tissue was reported in two lymph nodes along the left renal vessels of a 55-year-old woman with Crohn's disease.[7] The patient was found to have moderately differentiated adenocarcinoma of the ileocecal valve area and a benign renal oncocytoma.

An unusual case of heterotopic tissue was that of an angiomyolipoma present in both a para-aortic lymph node and the right kidney of a 42-year-old woman undergoing exploration for a right kidney mass.[9] The kidney and the lymph node had a similar histologic appearance.

Heterotopic tissue resembling colonic mucosa was seen in a mesenteric lymph node of a middle-aged woman undergoing left partial colectomy following excisional biopsy of an adenocarcinoma arising in a villous adenoma of the colon.[40] The tissue consisted of benign colonic mucosa cells, smooth-muscle cells, and a polymorphous mixture of inflammatory cells. No malignant cells were seen.

Mediastinum

Heterotopic tissue with unclassifiable histologic features was found in a mediastinal lymph node obtained at autopsy of an 87-year-old man who died of myocardial infarction.[9]

Neck

There were 39 patients with heterotopic tissue in cervical lymph nodes (Table 5). Their ages ranged from 14 to 84 years (mean, 45 years). Eighteen (90%) of 20 patients were male and the majority, 11 (73%) of 15, were operated on for benign disease. There were no reports of coexisting heterotopic tissue and metastatic disease.

There were several reports of thyroid follicles arising in lymph nodes,[12,41-45] but in only two was the entire thyroid gland subserially sectioned at 5-μm intervals to exclude an occult malignancy.[12,42] In one heterotopic thyroid, follicles were found in five of 106 autopsies.[12] Multiple lymph nodes were involved in two. The thyroids were subserially sectioned at 5-μm intervals. A single papillary carcinoma 2.2 mm in diameter was found in the contralateral lobe of one of these patients; the heterotopic tissue was not thought to represent a metastasis because it was unlikely to have metastasized to a contralateral lymph node.

In the other case, carcinoma was found arising in heterotopic thyroid tissue.[42] A papillary thyroid carcinoma was found in a left upper jugular lymph node in a 14-year-old girl. After total thyroidectomy, subserial sectioning of her entire thyroid gland at 5-μm intervals failed to reveal a primary site. Heterotopic parotid tissue has been reported in periparotid lymph nodes.[15,46] In 19 consecutive autopsies of infants, all were found to have normal parotid tissue in the periparotid lymph nodes.[15] Heterotopic parotid was seen in three lymphadenectomies for a neck mass and a fourth for melanoma. Heterotopic parotid tissue was seen in the periparotid lymph nodes of six patients with acquired immunodeficiency syndrome who were being evaluated for a neck mass.[46] The histologic features of this tissue appeared to be normal parotid. Two of these patients developed lymphoma after operation. In limited follow-up (1 to 3 years), three of the remaining patients did not develop clinical signs of malignancy. Heterotopic nevus cells were seen in patients operated on for laryngeal carcinoma,[47] epidermoid cyst,[48] and malignant melanoma.[5,11]

Axilla

There were 39 cases in axillary lymph nodes (Table 6). The ages ranged from 17 to 82 years (mean, 47 years), and 23 (59%) of 39 patients were women. Thirty-two (82%) of 39 were operated on for malignancy. In the patients operated on for benign disease, no follow-up data were available. There were five patients with heterotopic breast tissue. Only one was operated on for associated breast cancer.[49] The other four had benign breast lesions[10,49,50] or no breast disease.[51]

There have been 33 reports of benign nevus cells in axillary lymph nodes.[5,11,48,52] In one series, the incidence of nevus cells was 6.2% for patients undergoing axillary node dissections for breast cancer and malignant melanoma.[5] Coexistence of heterotopic tissue and metastatic disease was seen in two cases of malignant melanoma.[5] The nevus cells were easily distinguished from the metastatic disease by the benign appearance of the heterotopic tissue. There was one case report of unclassifiable benign glandular heterotopic tissue found in an axillary node of a 44-year-old woman who underwent a left modified radical mastectomy for infiltrating ductal carcinoma.[6]

COMMENT

Since the first report nearly a century ago,[53] heterotopic tissue has been reported in lymph nodes throughout the body.

In this review, there were a total of 289 cases of heterotopic tissue. The number of cases reported probably underestimates the actual incidence. While many cases have been reported, there have been surprisingly few prospective or retrospective series. In one series, heterotopic tissue was seen in pelvic lymph nodes of 14% of female autopsy specimens.[3] In another series, all of 19 consecutive autopsies of infants disclosed parotid tissue in periparotid lymph nodes.[15] These studies suggest that heterotopic tissue occurs more frequently than is currently known.

In this review, the most frequent site of occurrence was the pelvis (194 [67%] of 289), followed by the axilla (39 [13%] of 289), neck (39 [13%] of 289), groin (9 [3%] of 289), abdomen (7 [2%] of 289), and mediastinum (1 [<1%] of 289). The ages ranged from 8 to 87 years with a mean of 46 years (n = 102). Two hundred twenty-eight (84%) of 270 of the patients were women. Most cases have been reported in women due to the large number of reports of heterotopic tissue in pelvic lymph nodes obtained during operation for gynecologic disease. Heterotopic tissue was usually found incidentally during lymphadenectomies for other disease, most often malignancy. Frequently one or two lymph nodes were involved, but as many as three or more contained heterotopic tissue. Large nodules or cysts may enlarge the lymph node sufficiently to make it abnormal. Since this tissue is frequently found near malignant neoplasms in many instances, the possibility of this tissue representing metastatic disease cannot be entirely excluded.

In 214 (84%) of 255 cases, heteropic tissue was found in patients undergoing lymphadenectomy for malignancy. This is probably due to case selection. The histologic appearance of the heterotopic tissue was similar in patients operated on for either benign or malignant disease. Coexistence of heterotopic tissue and metastatic disease was reported in 12 patients. These tissues were easily distinguished because of the strikingly benign histologic appearance of the heterotopic tissue compared with the metastatic tissue. In addition, in three cases the malignancy was of squamous cell origin while the heterotopic tissue appeared glandular.

Heterotopic tissue in lymph nodes is site specific. For example, parotid tissue is seen in lymph nodes near the parotid gland, but not in the pelvis. This is in contrast to other instances of ectopic tissue not contained in lymph nodes; for example, adrenal tissue may be seen in the testes.[54] In these instances, the tissue is far removed from its normal anatomic position. The origin of heterotopic tissue in lymph nodes has been a matter of speculation. While several theories have been proposed to explain the histogenesis of heterotopic tissue at each site, a single unifying theory has not been accepted. Most of the discussion has focused on pelvic and cervical lymph node regions.

Several of the following theories have been proposed to explain the histogenesis of müllerian tissue in pelvic lymph nodes: (1) lymphatic spread[31,32]; (2) metaplasia of lymph node, subcoelomic mesenchyme, or peritoneal mesothelium[3,4,6,23,24,30]; (3) endometriosis[28]; and (4) admixture of lymph node cells and tissue during embryogenesis.[53] The most widely accepted theory for the histogenesis of müllerian heterotopic tissue is that of metaplasia of subcoelomic mesenchyme.[23,30] Although this is the most plausible theory, there are no studies that prove or disprove its basis. Furthermore, there may be more than one mechanism involved.

For heterotopic tissue in cervical lymph nodes, the most widely accepted theory is that an admixture of cells occurs during embryogenesis.[12,15] During development, lymph nodes are formed from lymph sacs at the same time that thyroid and parotid glands are migrating and developing.[56] It is possible, albeit unproven, that these tissues intermingle and result in heterotopic tissue in lymph tissue at that time.

Heterotopic tissue in lymph nodes is usually clinically silent except for those cases in which the lymph node enlarges sufficiently to be palpated or, as in one particular case, obstruct a ureter.[33] Very rarely, carcinoma has been reported to arise in heterotopic tissue.[26,42] In these cases it is very important to exclude the possibility of a primary tumor elsewhere.

There were a few reports of heterotopic tissue being mistaken for metastatic carcinoma. A 40-year-old woman underwent unnecessary chemotherapy and radiation therapy for what was thought to be recurrent breast cancer 5 years after a left modified radical mastectomy.[49] During a routine follow-up appointment 7 years later her pathologic report was reviewed and the diagnosis changed to heterotopic tissue in an axillary lymph node. A 20-year-old woman was diagnosed as having metastatic adenocarcinoma after appendectomy.[30] After exploratory laparotomy with lymph node and peritoneal biopsies, the diagnosis was changed to endosalpingosis with lymph node involvement. A 70-year-old woman with transitional cell carcinoma of the bladder underwent radical cystectomy and ileal conduit diversion.[36] Definitive pelvic lymph node dissection was not performed because the frozen section of a random lymph node biopsy showed metastatic adenocarcinoma. Permanent sections of the lymph node were diagnosed as heterotopic müllerian tissue.

On finding benign-appearing tissue in lymph nodes during lymph node biopsy or lymphadenectomy, several considerations should be given in the final diagnosis. First, heterotopic tissue is more common than expected, particularly in pelvic lymph nodes, and finding this tissue should not be dismissed as a rare entity. Second, in most instances this tissue is glandular, while the patient's primary disease may often be a squamous cell carcinoma. Third, frozen sections are inferior to permanent sections for establishing this diagnosis.[34] In cases in which the diagnosis is doubtful, consideration should be given to waiting for permanent sections before proceeding with definitive therapy. Finally, a wide variety of heterotopic tissues may be seen in lymph nodes and every effort should be made to exclude a primary malignancy at the suspected site. If this approach is followed and the occurrence of heterotopic tissue in lymph nodes is recognized, misdiagnosis can be avoided and appropriate therapy may be given.

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Discussion

ORLO H. CLARK, MD, San Francisco, Calif: When benign tissue in lymph nodes is mistaken for metastatic disease, unnecessary treatment may be used. It seems to me that heterotopic tissue most likely occurs as a result of an abnormality in embryogenesis.

The problem of heterotopic tissue situated in lymph nodes is not rare. Benign glandular inclusions were observed in 5% to 41% of patients operated on for gynecologic cancers and in 6.7% to 14% of all women at autopsy.[27] These glands resemble tubal and ovarian germal epithelium (distinguished from endometriosis by the absence of endometrial stroma) and appear to represent müllerian duct epithelium. Heterotopic thyroid tissue in cervical lymph nodes or "lateral aberrant thyroid" represents a more difficult clinical problem since metastatic papillary and follicular thyroid cancer can completely resemble normal thyroid tissue histologically. All of the patients I have treated with palpable nodes in the lateral neck containing thyroid tissue have had an occult or larger thyroid cancer in the ipsilateral side of the thyroid gland. It may be very difficult to distinguish between ectopic normal or malignant thyroid tissue because the thyroid tumors are so well differentiated. Heterotopic tissue usually occurs in normal-sized nodes and is typically situated at the periphery of the node.

Taptiklis (in 1967) gave intravenous injection of normal thyroid cells to mice and showed formation of intrapulmonary nodules of thyroid tissue that appeared histologically normal and also were stimulated by thyroid-stimulating hormone. Baker[56] documented that with advancing age, normal thyroid follicles in fish could invade other organs including kidney, spleen, eye, and brain. Luckily, this situation does not seem to occur clinically. Recent data suggest that breast tumors and melanomas that metastasize have an altered actin-fibronectin cystoskeletal system. Perhaps in the future, biochemical and immunohistochemical studies will help the pathologist and clinician distinguish between a well-differentiated metastatic tumor and benign heterotopic tissue in lymph nodes.

I do not accept the authors' conclusion of diagnosing thyroid tissue as ectopic when no lesion less than 5 μm in diameter is found in the thyroid. For example, would they use the same definition if the nodes were palpable and contained thyroid tissue? Do the authors think that ectopic nevi in lymph nodes may account for the 4% of patients who have melanoma in nodes, but no primary site is ever found? What is the authors' personal experience with this problem, especially near the pancreas?

BRUCE E. STABILE, MD, San Diego, Calif: I am concerned about some of the cases included in this series, specifically the lack of any real follow-up. Sawicki et al are making these definitions primarily on morphologic criteria, and morphologic and biologic behavior sometimes are inconsistent.

The other issue the authors should address is the fact that an overwhelming number of these cases occurred with lymph node dissections associated with malignant disease. Although many of the tissues found in lymph nodes were incompatible with the primary tumor resected, a number of them certainly were. Why do we have such a discrepancy between autopsy study material and the histologic material retrieved from surgical cases? Are we seeing cases that are being called heterotopic that really reflect occult malignancy or malignancy wherein the primary tumor regressed?

William B. Hutchinson, MD, Seattle, Wash: At the Surgical Cancer Consulting Service at the Pacific Northwest Research Foundation in Seattle, I saw an 18-year-old boy from Alaska a few years ago. He was a huge boy, very muscular, and had a 1-cm nevus on the skin of his left axilla. The node and the skin lesion had been removed by the surgeon in Alaska and interpreted as a metastatic melanoma. On our review of the slides, the lymph node was seen to contain only benign nevus cells within the node capsule. The skin lesion was a benign spindle and epithelioid nevus of the Spitz type. Observation rather than amputation was advised.

Donald E. Wagner, MD, Santa Monica, Calif: Was the heterotopic tissue primarily or always in the periphery of the lymph node and is this a good means of distinguishing between metastatic disease and primary disease? Have you had any documented cases of primary malignant neoplasms developing in this heterotopic tissue? I recently reviewed a patient who had a total mastectomy for prophylactic reasons 20 years ago and now has a lobular carcinoma in a lymph node on the same side.

Claude H. Organ, Jr, MD, Oakland, Calif: The lymphatics continue to be the system of mystery. I rise to bring up three specific cases related to Dr Passaro's presentation. First, regarding thyroid cancer, I subscribe to the concept that lymphatic tissue in lateral cervical nodes is pathognomonic of thyroid carcinoma until proven otherwise because this gland arises from a midline primordia. However, the parafollicular cells come from the ultimobranchial body, which is a lateral primordia. Theoretically, you can have normal thyroid tissue in the lateral cervical areas that might not represent carcinoma. For all practical purposes you have to consider it to be carcinoma until proven otherwise.

Second, I have seen two primary melanomas arise from lymph nodes after the $10 000 workup and biopsy of every skin lesion imaginable and all types of endoscopy failed to reveal a primary. These patients have had a long-term survival. We are aware of cases reported of a mother with melanoma in which a melanoma was present at birth in the infant; both died within the first year of life.

The third example is the nodal gastrinoma. I have observed hypergastrinemic patients considered to have a primary in the pancreas. At exploration, the lesion was found in a lymph node. The lymph node only was excised. They have returned to eugastrinemic levels. I have seen this twice and in each instance, the pancreas has been thoroughly explored, and contrary to what we all have been recently taught, we could find no identifiable tumor in the duodenum or elsewhere. Lymph nodes may produce tumors that can elaborate regulatory peptides and biogenic amines.

The apudoma concept has been uncritically accepted as fact. There is much supporting data that these tumors can arise from endodermal- and mesodermal-derived tissues. The Pearce concept of their ultrastructural characteristics is plausible. His evidence on the neural crest origin of these tumors is less compelling. Any cell in the body, with proper DNA programming, can be totipotential.

Dr Passaro, Jr: Our information about gastrinomas has evolved to where we understand that there is a species of gastrinoma called *nodal*, ie, contained solely within the lymph nodes. As Dr Stabile has pointed out, they occur in a certain area of the abdomen. We made a number of predictions to explain the presence of nodal gastrinomas. One was that in addition to the nodal gastrinomas, there should be heterotopic pancreatic tissue within lymph nodes found in the same areas, namely, on the right side of the abdomen.

We thought we could never get to address that question and did not expect there to be any relevant literature. The first thing that we found was that no one knew anything about heterotopic tissue in lymph nodes. The search in the literature revealed the following:

1. It was much more common than we had anticipated.
2. There was a preponderance of tissue in lymph nodes in women. Among men, there are no wolffian duct structures found within lymph nodes and they have been looked for prospectively. We have to explain the difference. Why are they so common in women, and why are they absent in men?
3. The true incidence of heterotopic tissue in lymph nodes is unknown; our study is retrospective. In a prospective study of 19 infants in which cervical parotid tissue was looked for, it was found in every case. That is striking.

We need to know if heterotopic tissue in lymph nodes is a very common event, if somewhere in the postnatal period, those tissues are allowed to die or regress, or are all swept away by the body.

The last point is about differentiation. Maybe the tissue contained within the lymph nodes has a level of differentiation or dedifferentiation that is different from its normal tissue counterpart. As a specific example, parotid tissue contained within lymph nodes may be dedifferentiated in contrast to normal parotid tissue. We are now at a level of sophistication, I think, in molecular biology to begin to address those questions.

Dr Clark, heterotopic tissue is more common than we suspect and in the vast majority of individuals, it probably regresses. Dr Organ, you have asked very important questions, both about thyroid cancer and nodal gastrinoma. In fact, as I have indicated, it was nodal gastrinoma that led us to investigate heterotopic tissue in lymph nodes. Dr Thomas, we do not know if these tumors arise as an intermingling of lymphoid tissue from metaplasia. I looked at it as representing an intermingling of lymphoid tissue, which is probably a common event. Dr Wagner, is heterotopic tissue always found at the periphery of the node? The answer is, very nearly always. There have been a few instances in which it has been found in the center of the node. Also, a malignancy has been noted within such nodes. Two case reports in the literature documented that.

There is no follow-up information with regard to these cases since these reports are found in the pathology literature. Why is it so infrequent at autopsy? I suspect that it is a sampling error in not asking the appropriate question.

Reoperative Surgery for the Morbidly Obese

A University Experience

Joe A. Cates, MD; Ernst J. Drenick, MD; Mohammed Z. Abedin, PhD; Jeff E. Doty, MD; Kimberly D. Saunders, MD; Joel J. Roslyn, MD

• Patients who undergo surgery for morbid obesity are often subjected to reoperation for a wide array of indications. To evaluate outcome following revisional procedures, we reviewed the records of 32 such patients treated at UCLA between April 1986 and May 1989. Twenty-five women (78%) and 7 men (22%) with a mean age of 44 years underwent 76 reoperations (2.4 per patient) for complications of prior obesity surgery. Indications for initial surgical revision consisted primarily of metabolic derangements (12 patients) and weight-related problems (11 patients). In contrast, indications for the patients' final surgical procedure were commonly for bowel obstruction (41%), intra-abdominal sepsis (12%), and gastrointestinal bleeding (6%). Following initial revision, 23 patients (71.8%) required further surgery for major complications and four patients died (12.5%). While initial revisions are frequently indicated for metabolic problems, final reoperations are more frequently undertaken for urgent, life-threatening complications. Revisional procedures for morbid obesity should be carefully considered, and the potential for major complications and/or death should be weighed heavily against proposed benefits.

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"Morbid obesity" refers to a specific subpopulation of obese individuals who weigh in excess of 200% of ideal weight or 45 kg over ideal body weight.[1,2] Because this unique condition has been associated with many systemic illnesses including hypertension, coronary artery disease, degenerative arthritis, diabetes, and others, morbid obesity has been itself recognized as a disease process.[3-6] In the United States, it is estimated that 4.5 million individuals or 5% of the adult population are morbidly obese.[1]

Inability to achieve satisfactory weight reduction coupled with the recognized decrease in life expectancy of the morbidly obese prompted an early interest in surgical intervention as an alternative means of therapy.[7-9] In 1978, a National Institutes of Health conference affirmed the role of surgery in selected patients with morbid obesity.[10] It was, however, suggested that these procedures should be restricted to patients in whom traditional therapy had failed. The proposed selection criteria limited candidates to morbidly obese patients who had been given suitable treatments of calorie restriction and/or behavioral therapy, but failed to improve or relapsed after short periods. Despite these apparently restrictive criteria, the number of bariatric procedures performed each year continues to increase. Depending on the procedure performed, various aspects of alimentary function are altered and a number of long-term complications may arise.[11-13] The reality of these sequelae, coupled with the uncertainty regarding adequacy of weight loss, has resulted in many obese patients undergoing revisional or "conversion" operations.[14-17] The aim of this study was to evaluate in a university setting the outcome of patients undergoing these reoperative bariatric procedures, and to define the scope of postoperative complications in this subset of patients.

PATIENTS AND METHODS

Study Design

A retrospective analysis was performed of all patients who underwent a bariatric procedure at UCLA Medical Center over the 37-month period from April 1986 to May 1989. Those patients undergoing a single successful bariatric procedure were excluded from further study. The study population included only those patients requiring one or more subsequent procedures for the management of complications related to the primary bariatric procedure. For the purpose of this review, the first reoperation has been designated as "initial revision." In those cases in which additional procedures were required, they have been classified as either "subsequent" or "final" procedures as appropriate. Following admission or transfer to UCLA, all patients were managed on a single resident teaching service supervised by some of us. The average length of patient follow-up from time of initial revision was 39 months. Postoperative complications were defined as any morbidity that prolonged hospitalization or caused readmission to the hospital. Revisional procedures were considered early if they occurred less than 1 year following primary bariatric procedure and late if they occurred thereafter. Data inquiry was based on total number and type of surgical procedures, indications for initial and subsequent surgeries, and postoperative complications and treatments.

Patient Population

From April 1986 to May 1989, 32 patients underwent reoperative bariatric procedures at UCLA and form the basis of this report. There were 25 women (78%) and seven men (22%) with an average age of 44 years (range, 30 to 58 years). These 32 patients underwent a total of 76 reoperations (2.4 per patient) for problems arising from their initial bariatric procedure. Nine patients (28%) of the study group had their initial bariatric procedure and all subsequent operations performed at UCLA. Twenty-three patients (72%) were re-

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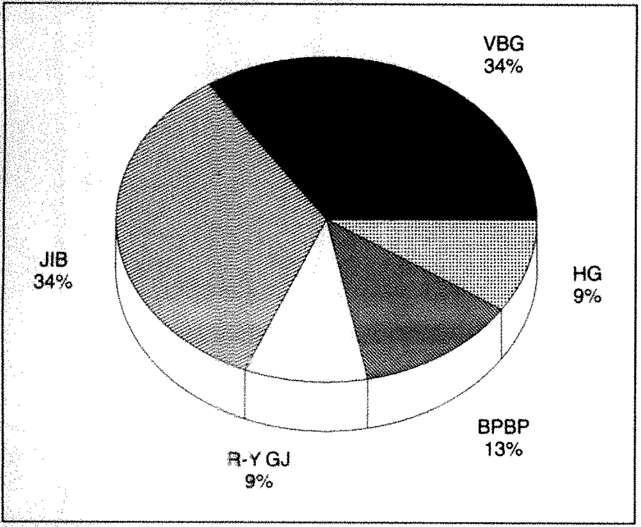

Fig 1.—Distribution of initial bariatric procedures. JIB indicates jejunoileal bypass; VBG, vertical banded gastroplasty; HG, horizontal gastroplasty; BPBP, biliopancreatic bypass; and R-Y GJ, Rou-en-Y gastrojejunostomy.

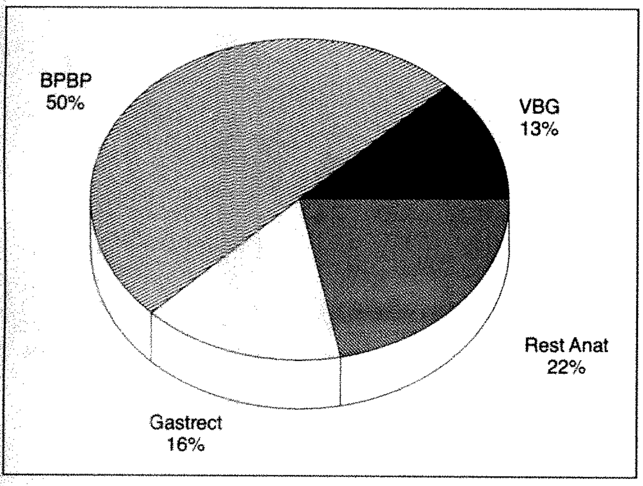

Fig 2.—Distribution of final or definitive operative procedures in the same patient population. BPBP indicates biliopancreatic bypass; VBG, vertical banded gastroplasty; Rest Anat, restoration of anatomic or physiologic gastrointestinal continuity; and Gastrect, subtotal or total gastrectomy.

ferred to UCLA for management of complications arising from a bariatric procedure. Only four patients underwent reoperation within the first year, and the remaining 28 (88%) patients had late reoperations, ie, more than 1 year after the primary bariatric procedure. The distribution of initial bariatric procedures (Fig 1) was as follows: jejunoileal bypass (JIB) in 11 patients (34%); vertical banded gastroplasty (VBG) in 11 patients (34%); biliopancreatic bypass (BPBP) in four patients (13%); and Roux-en-Y gastrojejunostomy (9%) and horizontal gastroplasty (9%) in two patients each). Figure 2 represents the distribution of final procedures on the same patients. Sixteen patients (50%) underwent BPBP, four patients (13%) VBG, five patients (16%) either subtotal or total gastrectomy, and seven patients (22%) were restored to physiologically "normal" anatomy. In patients restored to normal anatomy, gastrointestinal continuity was achieved via gastrogastrostomy (VBG, n = 2) or jejunojejunostomy (JIB, n = 2). In cases in which a BPBP was dismantled, the reconstruction consisted of a short Roux-en-Y gastrojejunostomy (n = 3). This latter procedure achieved nearly normal physiologic function. Anatomic restoration was not feasible since these three patients had undergone distal gastric resection as part of their primary BPBP.

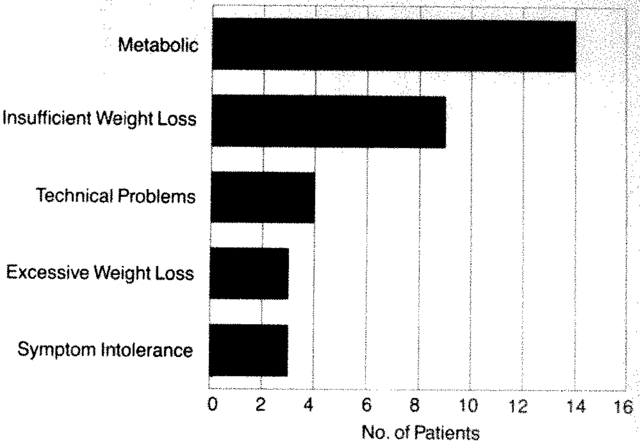

Fig 3.—Indications for revision of the patients' initial bariatric procedure. Although there were 32 patients in the series and therefore 32 initial reoperations, one patient had two indications for revision, thereby accounting for the 33 indications listed.

Indications for Surgical Revision Based on Primary Procedure*

	Type of Operation				
Indications	**JIB**	**H-G**	**GBP**	**VBG**	**BPBP**
Initial reoperation					
Metabolic	10	0	1	2	1
Insufficient weight loss	1	1	1	6	0
Excessive weight loss	1	0	0	1	1
Technical	0	0	0	2	2
Symptom intolerance	0	2	0	1	0
Subsequent reoperation					
Metabolic/weight-related	5	0	1	5	1
Bowel obstruction	5	3	0	3	2
Intra-abdominal sepsis	0	0	1	2	1
Enterocutaneous fistulae	0	0	1	1	0
Gastrointestinal bleeding	1	1	0	0	0

*Data are expressed in numbers of patients. JIB indicates jejunoileal bypass; H-G, horizontal gastroplasty; GBP, gastric bypass; VBG, vertical banded gastroplasty; and BPBP, biliopancreatic bypass.

RESULTS

Surgical Indications

The various indications for initial surgical revision of bariatric procedures in our study group are displayed in Fig 3. Metabolic complications were the primary indication in 44% of the patients studied. The most frequently cited problems included hyperuricemia, accelerated osteoarthritis, vitamin deficiencies, and renal lithiasis. Other reported indications included insufficient or excessive weight loss (total, 38%) and symptom intolerance (9%). Overall, 81% of the *initial* reoperations were performed for metabolic or weight-related problems. The reasons for the first reoperation and subsequent procedures were further separated according to the type of primary operation performed (Table). Metabolic problems were the predominant factor responsible for reoperation in patients who had undergone an initial JIB. In contrast, weight-related and technical problems led to reoperation in the study patients with an initial VBG. Overall, the indications for subsequent reoperation were vastly different as compared with indications for initial revision. The indications for subsequent reoperations included small-bowel obstruc-

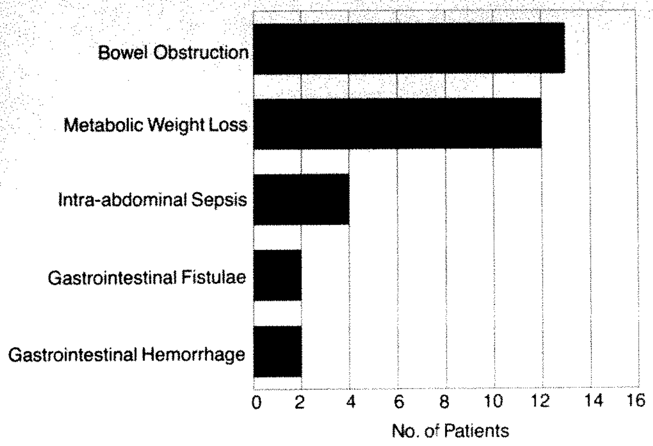

Fig 4.—Indications for final operative intervention in all 32 patients. As in Fig 3, one patient had two surgical indications.

tion, enterocutaneous fistulae, sepsis, and gastrointestinal hemorrhage. Within each operative category, the limited number of patients precludes more definitive analysis.

Figure 4 summarizes the frequency of indications for *final* procedures in the same 32 patients. Bowel obstruction was the surgical indication in 13 patients (41%), intra-abdominal sepsis in four patients (13%), and gastrointestinal hemorrhage and enterocutaneous fistulae in two patients each (12%). These indications represented life-threatening illnesses, and urgent surgery was required in most cases. Final operative procedures were undertaken for metabolic or weight-related problems in only 12 patients (38%).

Postoperative Complications

Seventy-six reoperations were performed following an initial bariatric procedure during the 37-month period of this study. Following initial revision, 23 (72%) of the 32 patients required further interventions for major complications. Of the nine patients who underwent a single revision, two (22%) died secondary to postoperative complications. The following tabulation summarizes the total number of postoperative complications that occurred during this time. There were 78 complications in all, and while metabolic complications were the most frequent, occurring in 18 patients (56%), 13 (41%) had major wound or intra-abdominal infectious complications. Forty percent of patients experienced a postoperative intestinal obstruction and 12 patients (38%) developed an incisional hernia. Pancreatitis, manifested clinically as an elevation in serum amylase and abdominal pain, was experienced by six patients (19%).

Type of Complication	No. of Patients
Reoperation	23
Metabolic	18
Infectious	13
Bowel obstruction	13
Hernia	12
Pancreatitis	6
Gastrointestinal bleeding	6
Cardiac	4
Central nervous system	2
Death	4

All of these individuals responded to conservative measures, and no pancreatic pseudocyst or abscess formation was reported. Cardiac complications consisted primarily of arrhythmias and contributed to one of the four reported mortalities. Two individuals experienced postoperative cerebrovascular accidents. Four (12.5%) of the patients undergoing revisional bariatric procedures died. Two patients died of intra-abdominal sepsis associated with multisystem organ failure after having been transferred to UCLA for complications related to their revisional procedure. One patient died of overwhelming septic shock and malnutrition after having been unavailable for follow-up. The final death occurred as a result of cardiac arrest in a patient who was recovering from a small-bowel resection for intestinal obstruction secondary to an internal hernia.

Seventy-two percent of all patients undergoing revisional bariatric procedures required further intervention for major gastrointestinal complications. Furthermore, 41% of all patients referred to UCLA following a bariatric procedure had a life-threatening illness that required urgent intervention. Among the patients with life-threatening complications, there were 3.5 complications per patient and the associated mortality rate was 25%. In contrast, the complication rate among patients undergoing elective admission was 1.4 per patient and there were no deaths in this group. Four patients died following surgical revision, constituting an overall mortality rate of 12.5%. Three of the four reported deaths occurred in patients who had undergone BPBP either as an initial weight-loss procedure or as a subsequent revision.

COMMENT

Bariatric surgery continues to be an evolving discipline. The ideal operation for the morbidly obese has yet to be identified and this whole area has been the focus of some controversy.[18] The alterations in normal gastrointestinal physiology produced by many of the currently performed procedures, in combination with the difficulty in predicting weight loss, is probably responsible for the number of patients who ultimately require some type of revision or reoperation. Data from the present study suggest that indications for initial surgical revision commonly include weight-related complaints or metabolic disorders. In contrast, when subsequent procedures are performed, the indications are generally much more serious. Furthermore, reoperation following revisional bariatric procedures is associated with significant morbidity and mortality.

During a 3-year period, 32 patients treated at UCLA underwent revisional surgery or reoperation following an initial bariatric procedure. Overall, 76 reoperations were performed in these patients for complications of prior obesity surgery. Postoperative morbidity was considerable in this group and the mortality rate was 12.5%. Three (75%) of the four deaths occurred in patients who had undergone a BPBP. While the death rate in the 16 patients who underwent some other form of bariatric procedure was 6.3%, the rate in patients undergoing reoperations following BPBP was 18.8%.

The frequency with which bariatric procedures are being performed in this country is unclear. Although the need for reoperation for insufficient or excessive weight loss or for associated metabolic disturbances is well recognized, it is nearly impossible to quantify the frequency with which this occurs. The risks associated with conversion surgery have recently been reviewed by Yale.[15] In this study, 120 patients undergoing conversion surgery between 1977 and 1987 were retrospectively analyzed. The early complication rate in this series was 18%, a figure similar to that reported by Linner[16] and Forse et al.[17] These authors concluded that conversion surgery is safe and effective. The results of our current study do not support this statement, but it may well be that we are talking about two very different patient populations. This is suggested by the large number of patients transferred to our institution with severe, potentially life-threatening problems. Undoubtedly, this observation reflects the tertiary referral nature of our practice. Additionally, previous reports have focused on revision of a gastric partitioning or JIB bypass to a gastric bypass, unbanded gastrogastrostomy, or VBG.[15-17] Conspicuously absent from these reports has been information dealing with patients who have undergone a BPBP. This procedure, first described by Scopinaro et al in 1976,[19] is being performed by a number of surgeons throughout this country. There is limited information, however, focusing on long-term outcome and complications associated with this procedure.

Some of the most catastrophic complications observed in the current series occurred in patients who had had a BPBP. Three patients with a functioning BPBP performed elsewhere underwent revisional procedures for metabolic or weight-related problems at an outside facility. All three patients had major complications with recurrent intra-abdominal sepsis and complex enterocutaneous fistulae. They were ultimately transferred to UCLA where, after lengthy hospitalizations in excess of 6 months each, two have undergone definitive reconstructive surgery. The third patient continues to have an enterocutaneous fistula and is being managed with home total parenteral nutrition. Two of these patients ultimately underwent takedown of their bypasses with physiologic (as opposed to anatomic) restoration of their gastrointestinal tracts. Four patients requiring reoperation following BPBP developed severe fungal sepsis, of which one died. The etiologic features of fungemia are not clear in this subgroup of patients, but it is interesting to speculate about the role of bacterial overgrowth in the biliary limb.

The vagaries of bariatric surgery suggest that revisional procedures will continue to be done until, perhaps, the "perfect" weight-reducing procedure is identified. It is difficult to identify specific criteria that should be used in the selection of an appropriate revisional procedure. This decision should be based on the surgeon's particular expertise, patient's previous procedures, current anatomy, eating habits, and overall medical condition. Although revisional or conversional surgery can generally be performed by experienced surgeons with minimal morbidity and mortality, one should be cognizant of the potential risks involved. Many of these patients, at the time of reoperation, are malnourished and not in optimal condition. Moreover, the anatomy of certain gastrointestinal arrangements may make dissection difficult and predispose patients to bacterial overgrowth secondary to "blind limbs." These factors should be carefully considered when contemplating reoperative surgery for the morbidly obese. While we accept the possibility that our population is very likely skewed, nonetheless, we must conclude that complications arising from reoperative bariatric procedures can be devastating. This appears to be particularly true for patients undergoing revision of a BPBP. In conclusion, our data suggest that revisional procedures for morbid obesity should be subjected to the utmost scrutiny, and the potential for major complications and/or death should be weighed heavily against proposed benefits.

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Discussion

BRUCE E. STABILE, MD, San Diego, Calif: The high morbidity and mortality attending late reoperation after weight-reducing surgery for the morbidly obese is often ignored. Since JIB operations are becoming more obsolete, relatively little information has been forthcoming on the late reoperation rates and risks following gastric bypass, gastroplasty, and the BPBP procedure. These operations have long-term failure rates and serious complications that have been minimized or not addressed at all. The true outcome data for these sometimes casually applied procedures would be particularly sobering. I remain to be convinced that bariatric surgery as widely practiced under the currently accepted eligibility criteria has durable benefits that clearly outweigh the perioperative and long-term mortality and morbidity. This is most particularly the case if one includes failure to sustain an acceptable weight loss among the numerous complications. Experience has shown that the laudable results from centers with particular interest and expertise in bariatric surgery are attributable in substantial part to the interest, expertise, and vigilance in the dietary management and counseling that postoperative patients receive for the duration of their lives.

Current investigations into the metabolism of adipocytes and the neuroendocrine control of appetite and satiety offer the promise of new nonsurgical approaches to both prevention and management. Specific regulatory abnormalities in triglyceride storage and mobilization and in plasma cholecystokinin levels have been identified in a variety of pathologic states including obesity, and therapeutic strategies are already being devised. It is disturbing that a surgical procedure as deforming and potentially morbid as the BPBP has evolved as treatment for a fundamentally metabolic or psychologic disorder. Hopefully, pharmacologic manipulations will relegate such high-risk operations to the bariatric museum shelf.

How often do patients require late surgical intervention for complications or failure of bariatric operations? Are these procedures being applied too casually and by unqualified practitioners? Is follow-up often grossly inadequate? The 41% rate of referred patients requiring urgent intervention raises the question of neglect or abandonment of these difficult patients who need lifelong attention and support.

Another issue is the extremely high rate of multiple reoperations and their attendant morbidity and mortality. Do the authors believe these results to be representative and expected? These data do not support the notion that bariatric surgery renders obese people safe for future operations.

Do the authors believe the BPBP to be a justifiable operation for morbid obesity? Do they accept the criterion of a body weight 45 kg over the ideal weight as a valid indication for a weight-reducing operation in the absence of other specific complications? Do they believe that the long-term salutary effects outweigh the combined total short- and long-term morbidity and mortality attending bariatric operations?

DAVID TAPPER, MD, Seattle, Wash: Thirty-four percent of the patients had JIBs. Was the operation performed as their only operation, or did they come from some other group? Were the complications uniform across the group? The patients with BPBPs had a substantial number but where did the complications, particularly the metabolic ones, relate to the JIB? Could you break the major and minor complications down? Were there wound complications such as hernias? Were they a result of wound infection?

CLAUDE H. ORGAN, JR, MD, Oakland, Calif: Many operations applauded in one decade have been discarded in the next. Bariatric surgery is such an example. The second most difficult decision in surgery is when to operate, the most difficult one being when to reoperate. These patients present a challenge for reoperation. The principal fault of bariatric surgery has been that the operations have been too easy. The jejunoileal bypass was too easy. The stapler made the gastric bypass easy. It was our experience that two thirds of the patients who came in for reoperation were malnourished but could be brought to a good nutritional state before reoperation. The biliary pancreatic bypass is a Mann-Williamson procedure (*Ann Surg.* 1923;77:409-422). It conforms very closely to what Mann and Williamson described from the Mayo Clinic in the 1920s. Why is there such a high percentage of bowel obstructions in these patients?

The second question has to do with the diabetic patient. What was your experience with diabetes? These are patients who have an incredible turnaround in their insulin requirements after surgery. Even before they left the hospital, some required no insulin, hypoglycemic agents, or dietary management. Did you have any experience with these groups, and were you reluctant to correct their bypass and return the gastrointestinal tract to normal?

DR ROSLYN: I hope that the general surgeons in the audience are interested in bariatric surgery, not necessarily as a clinical interest, but as an area that all general surgeons should be familiar with.

In an article in the September 1989 Bulletin of the American College of Surgeons, Lloyd McLean, MD clearly addresses many of the problems that deal with bariatric surgery as a discipline.

Dr Stabile, in the January 1990 issue of *Surgery*, Dr McLean suggests that in their series of 200 patients undergoing VBG, the reoperation rate was 36%. There truly are a large number of patients who undergo bariatric procedures and ultimately require reoperation. In most cases, the indication relates to insufficient or excessive weight loss.

It is hard for me to comment on follow-up. When we were actively doing bariatric procedures at our institution, the only way we would operate on any of these patients was if they were willing to be seen and followed up postoperatively by a specialist in metabolism.

Are these results representative, and how serious are some of these complications? Let me describe three of the more difficult patients who were treated in our series. A young lady underwent a VBG at an outside institution and developed a leak from her staple line. She was reoperated on several times and was finally transferred to UCLA in florid sepsis with a huge gastrocutaneous fistula. Subsequent tests done at UCLA demonstrated that she had a small pituitary tumor and that her obesity was really due to Cushing's disease. She died as a result of ongoing sepsis.

A second patient had a BPBP performed at an outside institution, and was reoperated on 20 months later because of problems with diarrhea. At reoperation, several enterotomies were made and she was ultimately transferred to UCLA with eight fistulas. She was hospitalized for 5 months before we were able to reconstruct her gastrointestinal tract by taking down her BPBP and restoring her normal anatomy.

The final patient had a BPBP performed in Italy. She came back to the United States and ultimately required takedown of her bypass revision. A gastroduodenostomy attempt resulted in anastomotic breakdown. She was transferred to UCLA with no abdominal wall and 16 fistulas. She was hospitalized for 8 months before her definitive surgery was done.

Dr Stabile, BPBP does achieve weight loss; but in terms of safety, it is still experimental, and further data are needed to establish its role. I will not address the issue as to whether patients who are morbidly obese should have bariatric procedures. If this discipline is to survive in the surgical world, it needs to focus on results not just in terms of weight loss; they need to look hard at results in terms of metabolic and postoperative complications.

Most of the bariatric procedures have become very easy. About half of the bowel obstructions were really gastric outlet obstructions and the remaining patients had small-bowel obstructions. All the small-bowel obstructions occurred in patients who had a BPBP. The very long distal Roux-en-Y gastrojejunostomy obviously has a great propensity for internal herniation. These operations are very effective in reversing diabetes in the morbidly obese patient. In my experience, a number of patients who were receiving 60 units or more of isophane insulin suspension per day were able, within 2 months, to have insulin therapy discontinued completely.

The last bariatric operation I performed was about 5 months ago. It was in a 131-kg physician who had such profound sleep apnea that he was dozing off while I was interviewing him in my office. Within 3 weeks after he was discharged from the hospital, he had absolutely no evidence of sleep apnea.

Dr Tapper asked about JIBs. All the patients undergoing a reoperation for JIB were referred from other institutions. We have not performed a JIB at UCLA in the last 14 to 15 years. Most of the catastrophic complications were in patients who had undergone a BPBP. Most of the wound complications were septic in nature and most of the hernias occurred in that setting.

At UCLA our experience with "virgin" bariatric procedures has really been limited because it has not been a major focus. The only patients that I see have had bariatric procedures and now have problems, not in terms of requiring revision for weight-related problems, but other sorts of problems.

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ACADEMIC TRAUMA/BURN SURGEON—Assistant or Associate Professor, in Residence, University of California, San Diego. The Department of Surgery is seeking an academic general/trauma/burn surgeon with experience in critical care who is board-certified or -eligible by the American Board of Surgery effective July 1, 1991. Qualifications: California medical license, demonstrated experience as a teacher and experience in research. Rank will be determined on the basis of experience and qualifications. Salary per UC scale. Send curriculum vitae and three letters of recommendation to: David B. Hoyt, MD, Chief, Division of Trauma, UCSD Medical Center, 225 Dickinson Street, San Diego, CA 92103. Closing date is December 13, 1990. UCSD is an affirmative action/equal opportunity employer.

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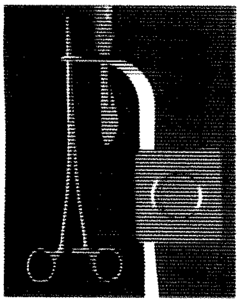

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CEFOTAN® IM/IV
(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).
Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.
Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.
Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).
Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus*.*
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

CEFOTAN® (cefotetan disodium)

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:}\quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:}\quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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References: **1.** Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

Please see adjacent page for brief summary of prescribing information.

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UCM

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Once for prophylaxis. Once daily for cure.

The prophylactic dose of ROCEPHIN is also the daily therapeutic dose. ROCEPHIN, 1 gm given once prior to surgery,* provides effective prophylaxis against infection and is on board throughout the perioperative period—even if surgery is delayed or prolonged.

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Once-a-day

Rocephin® IV·IM

ceftriaxone sodium/Roche

As with any cephalosporin, there exists the possibility of hypersensitivity reactions, especially in individuals with a history of sensitivity.

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* In contaminated or potentially contaminated procedures (*e.g.,* vaginal or abdominal hysterectomy), and for patients in whom infection at the operative site would present serious risk (*e.g.,* coronary artery bypass graft [CABG] surgery).

Please see adjacent page for summary of product information.

ROCEPHIN® (ceftriaxone sodium/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep. pneumoniae*, *Streptococcus* species (excluding enterococci), *Staph. aureus*, *H. influenzae*, *H. parainfluenzae*, *Klebsiella* species (including *K. pneumoniae*), *E. coli*, *E. aerogenes*, *Proteus mirabilis* and *Serratia marcescens*.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus*, *Staph. epidermidis*, *Streptococcus* species (excluding enterococci), *E. cloacae*, *Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*.

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli*, *Proteus mirabilis*, *Proteus vulgaris*, *M. morgani* and *Klebsiella* species (including *K. pneumoniae*).

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains.

PELVIC INFLAMMATORY DISEASE caused by *N. gonorrhoeae*.

BACTERIAL SEPTICEMIA caused by *Staph. aureus*, *Strep. pneumoniae*, *E. coli*, *H. influenzae* and *K. pneumoniae*.

BONE AND JOINT INFECTIONS caused by *Staph. aureus*, *Strep. pneumoniae*, *Streptococcus* species (excluding enterococci), *E. coli*, *P. mirabilis*, *K. pneumoniae* and *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS caused by *E. coli* and *K. pneumoniae*.

MENINGITIS caused by *H. influenzae*, *N. meningitidis* and *Strep. pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph. epidermidis* and *E. coli*.

SURGICAL PROPHYLAXIS: Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (*e.g.*, vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (*e.g.*, during coronary artery bypass surgery).

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery. When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure.

SUSCEPTIBILITY TESTING: Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, reported with nearly all antibacterial agents, including ceftriaxone, may range in severity from mild to life-threatening. Therefore, consider this diagnosis in patients who present with diarrhea subsequent to administration of antibacterial agents.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After establishing diagnosis of pseudomembranous colitis, initiate therapeutic measures. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consider management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug effective against *C. difficile*.

PRECAUTIONS: *GENERAL:* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.*, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

Rare cases reported of sonographic abnormalities seen in the gallbladder; patients may also have symptoms of gallbladder disease. These abnormalities, variously described as sludge, precipitations, echoes with shadows, may be misinterpreted as concretions. Chemical nature of sonographically-detected material not determined. Condition appears to be transient and reversible upon discontinuation of Rocephin and conservative management. Therefore, discontinue Rocephin if signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above develop.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

PREGNANCY: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

NURSING MOTHERS: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section. *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Rocephin should not be administered to hyperbilirubinemic neonates, especially prematures.

ADVERSE REACTIONS: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration.

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESTINAL—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

HEPATIC—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

RENAL—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%).

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%).

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours.

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days; in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone; piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone; bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION).

Also supplied as a sterile crystalline powder as follows:
ADD-Vantage Vials®* containing 1 gm or 2 gm equivalent of ceftriaxone.

Also supplied premixed as a frozen iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose plastic containers,† as follows:

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.9 gm dextrose hydrous, USP added.

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.2 gm dextrose hydrous, USP added.

NOTE: Rocephin in the frozen state should not be stored above -20°C

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†Manufactured for Roche Laboratories, a division of Hoffmann-La Roche Inc., by Travenol Laboratories, Inc., Deerfield, Illinois 60015.

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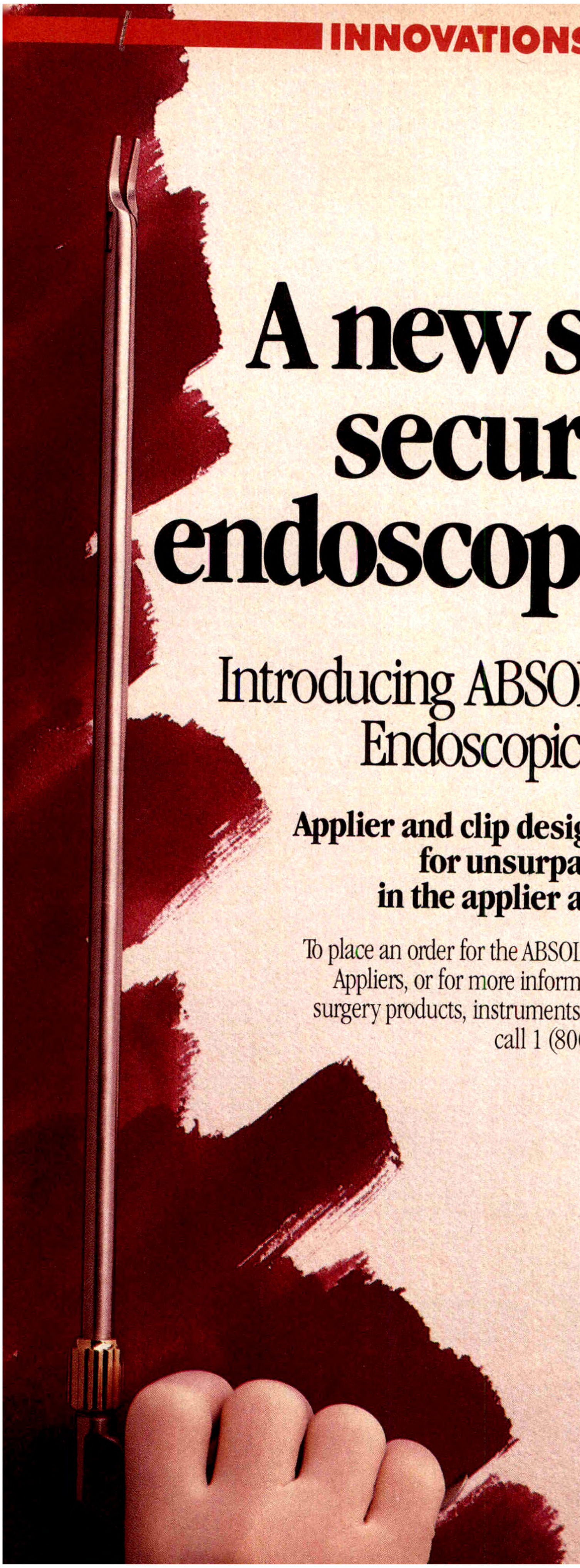

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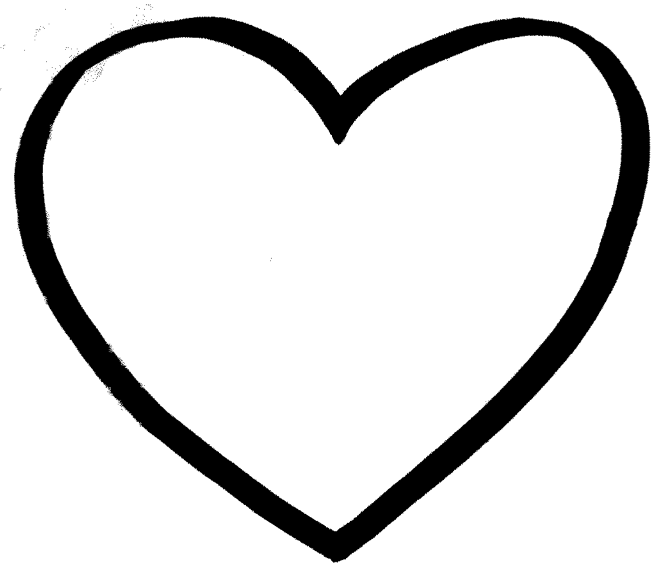

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INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain.
CONTRAINDICATIONS: Hypersensitivity to acetaminophen or hydrocodone.
WARNINGS:
Allergic-Type Reactions: VICODIN/VICODIN ES Tablets contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.
Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression.
Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.
PRECAUTIONS:
Special Risk Patients: VICODIN/VICODIN ES Tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.
Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when VICODIN/VICODIN ES Tablets are used postoperatively and in patients with pulmonary disease.
Drug Interactions: Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with VICODIN/VICODIN ES Tablets may exhibit an additive CNS depression. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.
Usage in Pregnancy:
Teratogenic Effects: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN/ VICODIN ES Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever.
Labor and Delivery: Administration of VICODIN/VICODIN ES Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN/VICODIN ES Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS:
The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include:
Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence and mood changes.
Gastrointestinal System: The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of VICODIN/VICODIN ES Tablets may produce constipation.
Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.
Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.
DRUG ABUSE AND DEPENDENCE:
VICODIN/VICODIN ES Tablets are subject to the Federal Controlled Substance Act (Schedule III). Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN/ VICODIN ES Tablets should be prescribed and administered with caution.
OVERDOSAGE:
Acetaminophen Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.
Hydrocodone Signs and Symptoms: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, (cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

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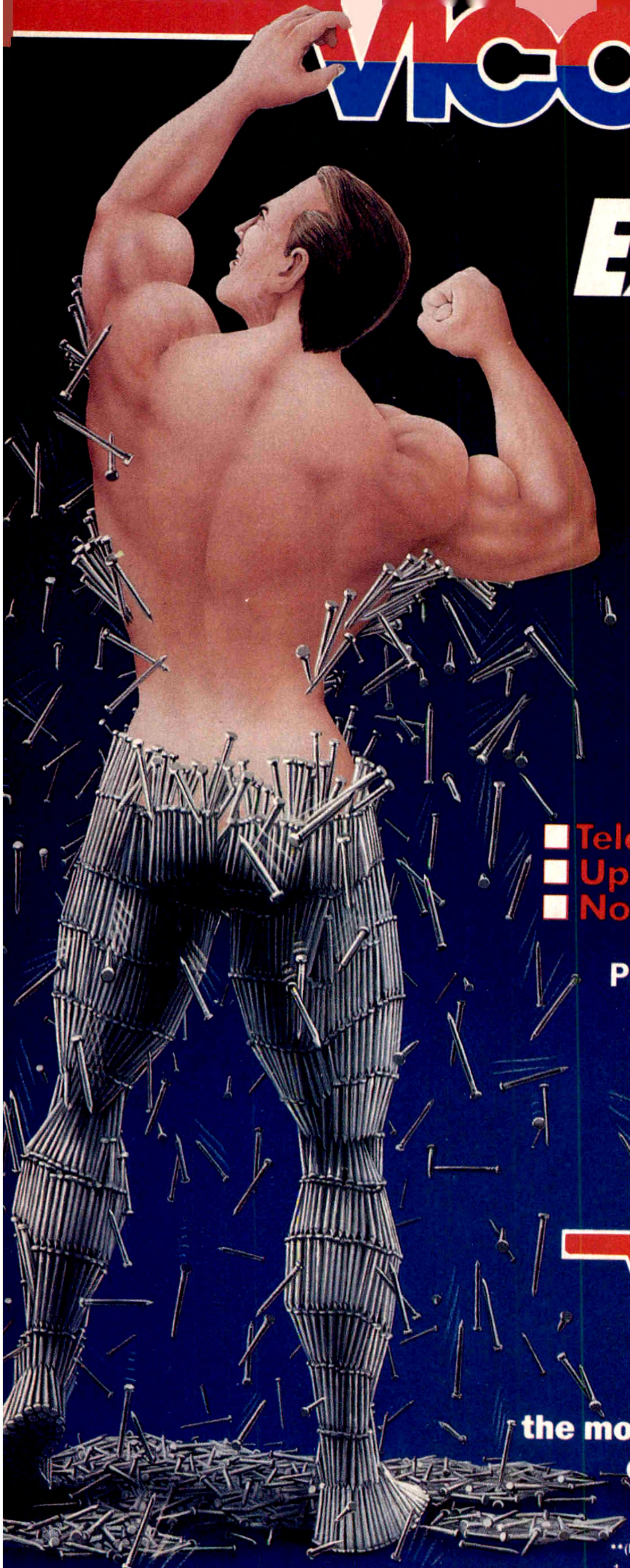

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1. Data on file, Knoll Pharmaceuticals
2. Standard industry new prescription audit.

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Archives of Surgery

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Extrahepatic Biliary Obstruction by Lymphoma 1507
Edward Feller, MD, Fred J. Schiffman, MD, Providence, RI
- Two patients with obstructive jaundice were satisfactorily palliated without operation when ERCP identified lymphoma as the cause.

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DISCHARGED

INTRAVENOUS

PRIMAXIN®

(Imipenem-Cilastatin Sodium|MSD)

A SUCCESSFUL TREATMENT OUTCOME FOR MANY PATIENTS*

*In one study, 90% of 135 patients with clinical signs of infection and two positive blood cultures were cured or improved (66% Cured, 24% Improved). Eron, L. J.: Imipenem/cilastatin therapy of bacteremia, Am. J. Med. *78(Suppl. 6A)*: 95-99, June 7, 1985.

PRIMAXIN is contraindicated in patients who have shown hypersensitivity to any component of this product. Before initiating therapy with PRIMAXIN, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams, and other allergens. If an allergic reaction to PRIMAXIN occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine and other emergency measures.

Please see Brief Summary of Prescribing Information.

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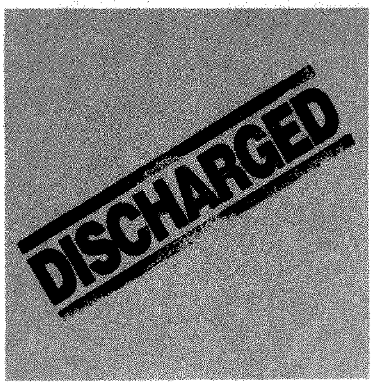

A SUCCESSFUL TREATMENT OUTCOME FOR MANY PATIENTS*

INTRAVENOUS

PRIMAXIN®

(Imipenem-Cilastatin Sodium|MSD)

*In one study, 90% of 135 patients with clinical signs of infection and two positive blood cultures were cured or improved (66% Cured, 24% Improved). Eron, L. J.: Imipenem/cilastatin therapy of bacteremia, Am. J. Med. 78(*Suppl. 6A*):95-99, June 7, 1985.

Contraindications: PRIMAXIN® (Imipenem-Cilastatin Sodium, MSD) is contraindicated in patients who have shown hypersensitivity to any component of this product.

Warnings: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA LACTAM. BEFORE INITIATING THERAPY WITH 'PRIMAXIN,' CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO 'PRIMAXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte, and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General* – CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

Patients with creatinine clearances of ≤5 mL/min/1.73 m^2 should not receive PRIMAXIN unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions – Generalized seizures have been reported in patients who received ganciclovir and PRIMAXIN. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility – Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN), and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Pregnancy – Pregnancy Category C: Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN® (Imipenem-Cilastatin Sodium, MSD) at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea, and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in nonpregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are under way to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use – Safety and effectiveness in infants and children below 12 years of age have not yet been established.

Adverse Reactions: PRIMAXIN is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions – Local adverse clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), infused vein infection (0.1%).

Systemic Adverse Reactions – The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were: nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal* – pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, hepatitis (rarely), gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS* – encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses* – transient hearing loss in patients with impaired hearing, tinnitus, taste perversion; *Respiratory* – chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular* – palpitations, tachycardia; *Skin* – toxic epidermal necrolysis (rarely), erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a Whole* – polyarthralgia, asthenia/weakness; *Renal* – acute renal failure (rarely), oliguria/anuria, polyuria. The role of PRIMAXIN in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

Adverse Laboratory Changes – Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic* – increased SGPT, SGOT, alkaline phosphatase, bilirubin, and LDH; *Hemic* – increased eosinophils, positive Coombs test, decreased WBC and neutrophils, including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes* – decreased serum sodium, increased potassium, increased chloride; *Renal* – increased BUN, creatinine; *Urinalysis* – presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

NOTE: Due to the high antimicrobial activity of PRIMAXIN, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

How Supplied: PRIMAXIN is supplied as a sterile powder mixture in vials, infusion bottles, and single-dose ADD-Vantage®† vials containing imipenem anhydrous and cilastatin sodium as follows: 250 mg imipenem equivalent and 250 mg cilastatin equivalent; 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

Caution: The suspension from vials is not for direct infusion.

†Registered trademark of Abbott Laboratories, Inc.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486 *J9PR40(410)*

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NOW: REASON TO REFER
VIRTUALLY EVERY PATIENT
AFTER RESECTION OF
DUKES' C COLON CANCER

**PROVEN TO REDUCE
RISK OF RECURRENCE
41%[1]**

In a 5½-year, cooperative, randomized trial of 929 Dukes' C patients after surgical resection:

ERGAMISOL® + 5-FU significantly increased overall survival and reduced tumor recurrences

Regimen well-tolerated; adverse reactions "did not greatly impede patients' compliance with their regimen"[1]

NEW
ERGAMISOL®
LEVAMISOLE HCl TABLETS
in combination with 5-fluorouracil

**Considered
Today's Standard**

JANSSEN
PHARMACEUTICA

Reference: 1. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *New Engl J Med.* 1990;322:352-358.

Please see brief summary of prescribing information on next page.

ERGAMISOL® (Levamisole Hydrochloride) Tablets

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE: ERGAMISOL (levamisole hydrochloride) is only indicated as adjuvant treatment in combination with fluorouracil after surgical resection in patients with Dukes' stage C colon cancer.

CONTRAINDICATIONS: ERGAMISOL (levamisole hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or its components.

WARNINGS: ERGAMISOL (levamisole hydrochloride) has been associated with agranulocytosis, sometimes fatal. The onset of agranulocytosis is frequently accompanied by a flu-like syndrome (fever, chills, etc.); however, in a small number of patients it is asymptomatic. A flu-like syndrome may also occur in the absence of agranulocytosis. It is essential that appropriate hematological monitoring be done routinely during therapy with ERGAMISOL and fluorouracil. Neutropenia is usually reversible following discontinuation of therapy. Patients should be instructed to report immediately any flu-like symptoms.

Higher than recommended doses of ERGAMISOL may be associated with an increased incidence of agranulocytosis, so the recommended dose should not be exceeded.

The combination of ERGAMISOL and fluorouracil has been associated with frequent neutropenia, anemia and thrombocytopenia.

PRECAUTIONS: Before beginning this combination adjuvant treatment, the physician should become familiar with the labeling for fluorouracil.

Information for Patients: The patient should be informed that if flu-like symptoms or malaise occurs, the physician should be notified immediately.

Drug Interactions: ERGAMISOL (levamisole hydrochloride) has been reported to produce "ANTABUSE®"-like side effects when given concomitantly with alcohol. Concomitant administration of phenytoin and ERGAMISOL plus fluorouracil has led to increased plasma levels of phenytoin. The physician is advised to monitor plasma levels of phenytoin and to decrease the dose if necessary.

Laboratory Tests: On the first day of therapy with ERGAMISOL/fluorouracil, patients should have a CBC with differential and platelets, electrolytes and liver function tests performed. Thereafter, a CBC with differential and platelets should be performed weekly prior to each treatment with fluorouracil with electrolytes and liver function tests performed every 3 months for a total of one year. Dosage modifications should be instituted as follows: If WBC is 2500-3500/mm^3 defer the fluorouracil dose until WBC is $>$ 3500/mm^3. If WBC is $<$ 2500/mm^3, defer the fluorouracil dose until WBC is $>$ 3500/mm^3; then resume the fluorouracil dose reduced by 20%. If WBC remains $<$ 2500/mm^3 for over 10 days despite deferring fluorouracil, discontinue administration of ERGAMISOL. Both drugs should be deferred unless enough platelets are present ($\geq$ 100,000/mm^3).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate animal carcinogenicity studies have not been conducted with levamisole. Studies of levamisole administered in drinking water at 5, 20, and 80 mg/kg/day to mice for up to 18 months or administered to rats in the diet at 5, 20, and 80 mg/kg/day for 24 months showed no evidence of neoplastic effects. These studies were not conducted at the maximum tolerated dose, therefore the animals may not have been exposed to a reasonable drug challenge. No mutagenic effects were demonstrated in dominant lethal studies in male and female mice, in an Ames test, and in a study to detect chromosomal aberrations in cultured peripheral human lymphocytes.

Adverse effects were not observed on male or female fertility when levamisole was administered to rats in the diet at doses of 2.5, 10, 40, and 160 mg/kg. In a rat gavage study at doses of 20, 60, and 180 mg/kg, the copulation period was increased, the duration of pregnancy was slightly increased, and fertility, pup viability and weight, lactation index, and number of fetuses were decreased at 60 mg/kg. No negative reproductive effects were present when the offspring were allowed to mate and litter.

Pregnancy: Pregnancy Category C: Teratogenicity studies have been performed in rats and rabbits at oral doses up to 180 mg/kg. Fetal malformations were not observed. In rats, embryotoxicity was present at 160 mg/kg and in rabbits, significant embryotoxicity was observed at 180 mg/kg. There are no adequate and well-controlled studies in pregnant women and ERGAMISOL should not be administered unless the potential benefits outweigh the risks. Women taking the combination of ERGAMISOL and fluorouracil should be advised not to become pregnant.

Nursing Mothers: It is not known whether ERGAMISOL is excreted in human milk; it is excreted in cows' milk. Because of the potential for serious adverse reactions in nursing infants from ERGAMISOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ERGAMISOL in children have not been established.

ADVERSE REACTIONS: Almost all patients receiving ERGAMISOL (levamisole hydrochloride) and fluorouracil reported adverse experiences. Tabulated below is the incidence of adverse experiences that occurred in at least 1% of patients enrolled in two clinical trials who were adjuvantly treated with either ERGAMISOL or ERGAMISOL plus fluorouracil following colon surgery. In the larger clinical trial, 66 of 463 patients (14%) discontinued the combination of ERGAMISOL plus fluorouracil because of adverse reactions. Forty-three of these patients (9%) developed isolated or a combination of gastrointestinal toxicities (e.g. nausea, vomiting, diarrhea, stomatitis and anorexia). Ten patients developed rash and/or pruritus. Five patients discontinued therapy because of flu-like symptoms or fever with chills; ten patients developed central nervous system symptoms such as dizziness, ataxia, depression, confusion, memory loss, weakness, inability to concentrate, and headache; two patients developed reversible neutropenia and sepsis; one patient because of thrombocytopenia; one patient because of hyperbilirubinemia. One patient in the ERGAMISOL plus fluorouracil group developed agranulocytosis and sepsis and died.

In the ERGAMISOL alone arm of the trial, 15 of 310 patients (4.8%) discontinued therapy because of adverse experiences. Six of these (2%) discontinued because of rash, six because of arthralgia/myalgia, and one each for fever and neutropenia, urinary infection, and cough.

For medical questions, call 1-800-253-3682 (9 AM-5 PM Eastern Time).

Adverse experience	ERGAMISOL N = 440 %	ERGAMISOL plus fluorouracil N = 599 %
Gastrointestinal		
Nausea	22	65
Diarrhea	13	52
Stomatitis	3	39
Vomiting	6	20
Anorexia	2	6
Abdominal pain	2	5
Constipation	2	3
Flatulence	<1	2
Dyspepsia	<1	1
Hematological		
Leukopenia		
$<$2000/mm^3	<1	1
$\geq$2000 to $<$4000/mm^3	4	19
$\geq$4000/mm^3	2	33
unscored category	0	<1
Thrombocytopenia		
$<$50,000/mm^3	0	0
$\geq$50,000 to $<$130,000/mm^3	1	8
$\geq$130,000/mm^3	1	10
Anemia	0	6
Granulocytopenia	<1	2
Epistaxis	0	1
Skin and Appendages		
Dermatitis	8	23
Alopecia	3	22
Pruritus	1	2
Skin discoloration	0	2
Urticaria	<1	0
Body as a Whole		
Fatigue	6	11
Fever	3	5
Rigors	3	5
Chest pain	<1	1
Edema	1	1
Resistance Mechanisms		
Infection	5	12
Special Senses		
Taste Perversion	8	8
Altered sense of smell	1	1
Musculoskeletal System		
Arthralgia	5	4
Myalgia	3	2
Central and peripheral nervous system		
Dizziness	3	4
Headache	3	4
Paresthesia	2	3
Ataxia	0	2
Psychiatric		
Somnolence	3	2
Depression	1	2
Nervousness	1	2
Insomnia	1	1
Anxiety	1	1
Forgetfulness	0	1
Vision		
Abnormal tearing	0	4
Blurred vision	1	2
Conjunctivitis	<1	2
Liver and biliary system		
Hyperbilirubinemia	<1	1

In worldwide experience with ERGAMISOL, less frequent adverse experiences included exfoliative dermatitis, periorbital edema, vaginal bleeding, anaphylaxis, confusion, convulsions, hallucinations, impaired concentration, renal failure, elevated serum creatinine, and increased alkaline phosphatase. An encephalopathy - like syndrome has been reported in patients treated with ERGAMISOL.

The following additional adverse experiences have been reported for fluorouracil alone: esophagopharyngitis, pancytopenia, myocardial ischemia, angina, gastrointestinal ulceration and bleeding, anaphylaxis and generalized allergic reactions, acute cerebellar syndrome, nystagmus, dry skin, fissuring, photosensitivity, lacrimal duct stenosis, photophobia, euphoria, thrombophlebitis, and nail changes.

HOW SUPPLIED: ERGAMISOL (levamisole hydrochloride) is available in white, coated tablets containing the equivalent of 50 mg of levamisole base, debossed "JANSSEN" and "L"
"50."

They are supplied in blister packages of 36 tablets (NDC 50458-270-36).

Store at room temperature, 15°-30°C (59°-86°F). Protect from moisture.

IN DUKES' C COLON CANCER

50 mg

ERGAMISOL
LEVAMISOLE HCl TABLETS
in combination with 5-fluorouracil

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Edition June, 1990 7500100-M U.S. Patent Number 4,584,305

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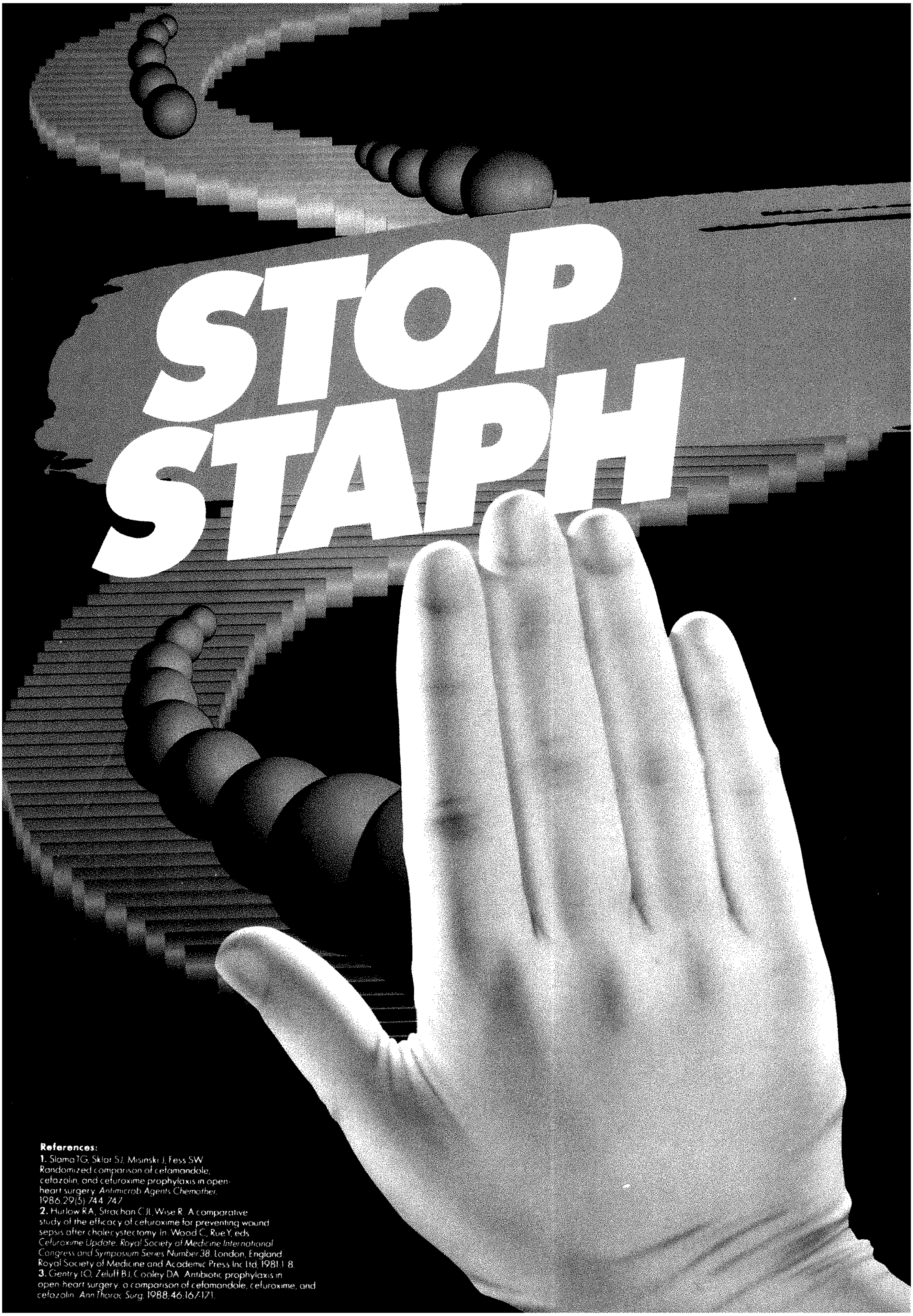

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2. Hurlow RA, Strachan CJL, Wise R. A comparative study of the efficacy of cefuroxime for preventing wound sepsis after cholecystectomy. In: Wood C, Rue Y, eds. *Cefuroxime Update. Royal Society of Medicine International Congress and Symposium Series Number 38.* London, England: Royal Society of Medicine and Academic Press Inc Ltd; 1981:1-8.
3. Gentry LO, Zeluff BJ, Cooley DA. Antibiotic prophylaxis in open-heart surgery: a comparison of cefamandole, cefuroxime, and cefazolin. *Ann Thorac Surg.* 1988;46:167-171.

Effective Staph Reduction

ZINACEF® IM/IV GLAXO

sterile cefuroxime sodium

- Outstanding protection against postsurgical staphylococcal infections[1]
- More effective surgical prophylaxis* than cefazolin[1,2]
- Beta-lactamase stability superior to cefazolin[2]
- More convenient, economical dosing than cefazolin[3]

*In clean-contaminated or potentially contaminated surgical procedures.

For a complete listing of indications and usage, please consult Brief Summary of Prescribing Information for ZINACEF on adjacent page.

Glaxo Pharmaceuticals™
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

Zinacef* **(sterile cefuroxime sodium, Glaxo)** **Zinacef*** **(cefuroxime sodium injection)** **BRIEF SUMMARY**

The following is a brief summary only. Before prescribing, see complete prescribing information in Zinacef* product labeling.

INDICATIONS AND USAGE: Zinacef* is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases.

1. **Lower Respiratory Tract Infections**, including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp, *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing), *Streptococcus pyogenes*, and *Escherichia coli*.
2. **Urinary Tract Infections** caused by *E coli* and *Klebsiella* spp.
3. **Skin and Skin Structure Infections** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, *E coli*, *Klebsiella* spp, and *Enterobacter* spp.
4. **Septicemia** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pneumoniae*, *E coli*, *H influenzae* (including ampicillin-resistant strains), and *Klebsiella* spp.
5. **Meningitis** caused by *S pneumoniae*, *H influenzae* (including ampicillin-resistant strains), *Neisseria meningitidis*, and *S aureus* (penicillinase- and non-penicillinase-producing).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *S aureus* (including penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Zinacef has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to Zinacef.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Zinacef may be used concomitantly with an aminoglycoside (see PRECAUTIONS). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of Zinacef may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (eg, vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Zinacef should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of Zinacef has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that Zinacef therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS: Zinacef* is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH ZINACEF* IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: Although Zinacef* rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of Zinacef should be reduced in patients with transient or persistent renal insufficiency (see DOSAGE AND ADMINISTRATION), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of Zinacef may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Drug/Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest* tablets), but not with enzyme-based tests for glycosuria (eg, Tes-Tape*). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving Zinacef.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since Zinacef is excreted in human milk, caution should be exercised when Zinacef is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS: Zinacef* is generally well tolerated. The most common adverse effects have been local reactions following intravenous administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with intravenous administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in less than 1% of the patients treated with Zinacef and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in less than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (less than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Toxic epidermal necrolysis, fever, vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Prolonged prothrombin time, pancytopenia, agranulocytosis, thrombocytopenia.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zinacef* product labeling.)

Impaired Renal Function: A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see Table 1 in product package insert).

HOW SUPPLIED: Zinacef* in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected from light. Zinacef is a dry, white to off-white powder supplied in vials and infusion packs as follows:

NDC 0173-0352-31 750-mg† Vial (Tray of 25)
NDC 0173-0354-35 1.5-g† Vial (Tray of 25)
NDC 0173-0353-32 750-mg† Infusion Pack (Tray of 10)
NDC 0173-0356-32 1.5-g† Infusion Pack (Tray of 10)
NDC 0173-0400-00 7.5-g† Pharmacy Bulk Package (Tray of 6)

Zinacef frozen as a premixed solution of cefuroxime sodium should not be stored above −20°C. Zinacef is supplied frozen in 50-ml, single-dose, plastic containers as follows:

NDC 0173-0424-00 750-mg† Plastic Container (Carton of 24)
NDC 0173-0425-00 1.5-g† Plastic Container (Carton of 24)

† Equivalent to cefuroxime.

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DIVISION OF GLAXO INC
Research Triangle Park, NC 27709

Zinacef* (sterile cefuroxime sodium): Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
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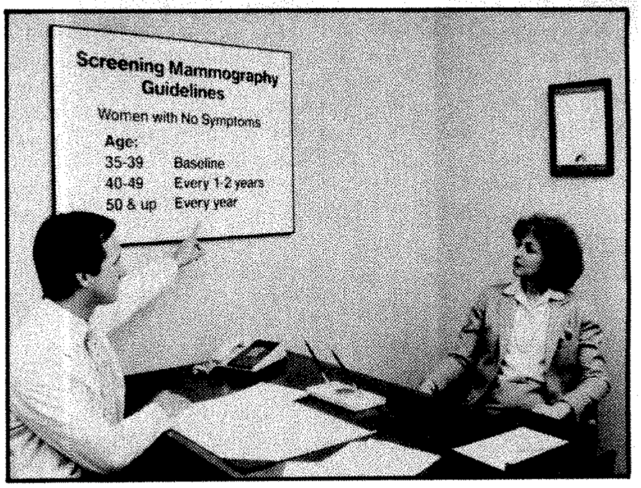

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Nobel Laureate: Joseph E. Murray, Clinical Surgeon, Scientist, Teacher

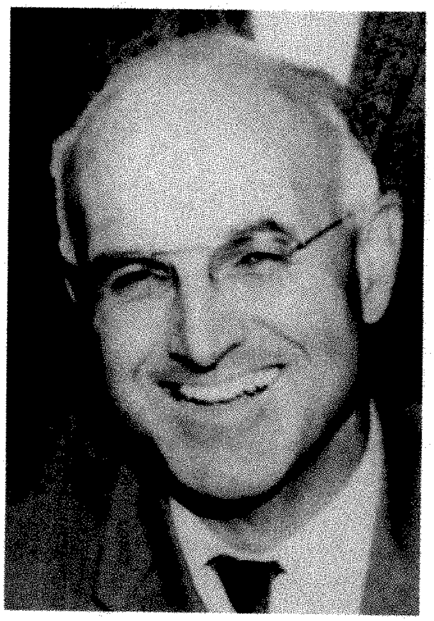
On Monday, October 8, 1990, the Clinical Congress of the American College of Surgeons and the surgical community at large were elated by the announcement that the Nobel Committee had awarded the 1990 Prize for Medicine or Physiology to Joseph E. Murray, MD, of Brigham and Women's Hospital in Boston, Mass, and to E. Donnall Thomas, MD, of the Fred Hutchinson Cancer Center, Seattle, Wash, for their discoveries enabling organ and cell transplantation. Dr Murray performed the first successful transplantation of a kidney from a living donor in identical twins. Subsequently, he demonstrated the feasibility of cadaveric kidney transplantation by ameliorating the immune response initially with radiation and subsequently with drug therapy, notably azathioprine and steroids. Dr Thomas demonstrated that methotrexate likewise would ameliorate the graft-vs-host response in bone marrow transplantation. This work was the seminal research that not only established organ transplantation, a human dream from the time of the early Church and the legend of Saints Cosmos and Damien, as clinical reality, but also gave impetus to intense and productive study of the biology of the immune response.

"Real talent is pure gold. Brilliant research capability, or the ability to inspire and teach, or outstanding clinical skills: rarely are all three in one individual, nor does that matter in a well-balanced institution. Institutional balance requires vision, riches, space."[1] That Harvard University has vision, riches, and space enough, most would agree. However, individuals like Joseph Murray, pure gold, are uncommon.

Joseph Murray clearly is real talent. His research capability, although always acknowledged and recognized by his peers in the surgical community, has now been accorded the ultimate prize in science. The initial work required surpassing clinical skills as well as fundamental scientific inquiry. Moreover, there was scrupulous attention to the moral and ethical considerations of subjecting a healthy normal human to an extensive surgical procedure to benefit an ill relative dying of chronic renal disease.

Joseph Murray is a superb clinical surgeon. The technical details of renal transplantation have undergone subtle refinements over the years, but the essentials of that remarkable operation have remained intact since it was devised by Dr Murray with the assistance of a urologic colleague, J. Hartwell Harrison.

Joseph Murray is a generalist, even rarer in the modern university than the triple-threat academician. "Unbridled specialization is higher education's mortal sickness leading to atomistic narrowness and incoherence."[2] Ever increasing specialization has been rationalized as inevitable because of the expanding universe of knowledge. Specialization, of and by itself, may well be inevitable for the reasons given, but the fragmentation and attendant evils that follow in its wake need not be. One can and should direct energy and talent in a focused manner, lest they dissipate with little trace. The focus of a surgical specialist, however, should not gainsay genuine interest in the entire field of surgery, nor in continued acquisition of general knowledge—the mark of an educated individual. The paradigm of an educated surgeon is Joseph Murray.



Joseph E. Murray, MD, in 1965

After graduating from Harvard Medical School in 1943, Joseph Murray interned at Peter Brigham Hospital in Boston. The war years, however, interrupted his residency. He was assigned by the US Army to Valley Forge Hospital, which was a center for the reconstruction of form and function in the wounded of World War II. There he acquired the skills of plastic surgery, exposed to men like James Barrett Brown of St Louis, Mo, Bradford Cannon of Boston, Carl Lischer of St Louis, Andrew Moore of Lexington, and others. These skills he honed in that intense experience. After the war he completed his surgical residency at the Brigham Hospital. Dr Murray then had a fellowship in head and neck surgery at the Memorial Sloan Kettering Hospital, New York, NY, followed by an additional year of plastic surgery training at New York Hospital. He then returned to the Brigham Hospital to begin his work in the surgical research laboratory in transplantation. While his avocation was transplantation, his vocation was plastic and reconstructive surgery. The bridge between the two was burn wound coverage and skin homografting. The original twin pair in whom the kidney transplant operation was performed had their monozygosity established by full-thickness skin grafting—a technique originally reported by James Barrett Brown.[3]

In the 1950s both the medical service and the surgical service at the Brigham Hospital were very much engaged in finding ways to treat end-stage renal disease, then universally fatal. A kidney dialysis machine was conceived by Willem Kolff, Carl Walter, and engineer Edward Olson. John Merrill began the dialysis care of these chronically ill patients (*Harvard Medical Area Focus*, October 11, 1990:1-5). Dr Murray, a fledgling assistant clinical professor of surgery, began studies directed toward breaching the immunogenetic barrier to make renal transplantation possible. Basic studies were carried out in mice, rabbits, and dogs. Hundreds of experiments were carried out in dogs, the practical animal model closest to the human, to develop not only the surgical transplantation technique, but methods of immunosuppression, induction of tolerance, and adaptation.[4] After much preliminary and thorough experimental work in animals, the first successful human renal transplant was carried out in identical twins on December 23, 1954.[5]

While the renal transplantation work was going on, Dr Murray built a clinical practice in plastic surgery and made significant contributions to head and neck oncology. He and Donald Matson, Chief of Neurosurgery at Brigham and Children's hospitals, combined their skills to develop a craniofacial approach to orbital tumors in children. Their work, along with that of Paul Tessier in France and John Converse and Milton Edgerton in the United States, demonstrated the feasibility, safety, and accuracy of craniofacial surgery and clearly established craniofacial surgery as a subspecialty of surgery.

Following the retirement of Donald McCollum, attending plastic surgeon at the Brigham and Childrens Hospitals, Dr Murray was appointed chief of that division. He not only enlarged the scope and diversity of plastic surgery at those institutions, but also established a postgraduate training program in plastic surgery, the first such residency program in Boston. It quickly acquired a deserved reputation for excellence because of Dr Murray's skills as a teacher and his example as a clinical surgeon and investigator.

His legacy to humankind: a definitive answer to end-stage renal disease, a powerful stimulus to basic immunologic research worldwide, craniofacial reconstruction, character, and kindness. His legacy to surgery: two entirely new fields of surgery, the stimulus and inspiration for numerous leaders of surgery not only in this country but throughout the world, and the model of an educated surgeon.

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Atlanta, Ga

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Special Article

On the Supply of Physicians

Peter I. Buerhaus, PhD, RN, George D. Zuidema, MD

• The congressionally created Council of Graduate Medical Education is conducting a study to assess the adequacy of the current and future supply of physicians in six specialties. The study is revising and updating the needs-based method used by the Graduate Medical Education National Advisory Committee and using this method to project the requirements for physicians for the next two decades. Projections on the supply of physicians will be based on the latest data from the federal government's Bureau of Health Profession's health manpower model. Previous physician manpower studies are reviewed to provide a historic perspective and a frame of reference for the variables, data sources, and assumptions being considered by the Council of Graduate Medical Education study.

(*Arch Surg.* 1990;125:1425-1429)

In 1987, Congress created the Council on Graduate Medical Education (COGME) to provide advice and recommendations on issues concerning the current and future adequacy of physician supply and financing of graduate medical education.[1] In July 1988, COGME issued its first report and with respect to the supply of physicians concluded that:

> . . .there is now or soon will be an aggregate oversupply of physicians in the United States. . . . There are significant uncertainties which could change this assessment . . . and there is conflicting evidence as to whether an oversupply of physicians would necessarily lead to socially undesirable consequences.[1(p71)]

In light of these conclusions, COGME recommended that:

> At the present time, the federal government should not attempt to influence physician supply in the aggregate . . . and that the number of first-year positions in graduate medical education should not be used to reduce the supply of licensed physicians in the aggregate; rather, if steps are taken to reduce physician supply, the reduction should take place in entering medical school class size.[1(pp72,73)]

This article describes the study that COGME's Subcommittee on Physician Manpower is conducting to determine the adequacy of the future supply of physicians. Preceding this description, a review of previous manpower studies is provided to help place COGME's study within the broader context of physician manpower planning and to acquaint the reader with some of the variables, assumptions, and issues that the study is confronting.

EARLY PHYSICIAN MANPOWER STUDIES

Although Flexner's historic report[2] to the Carnegie Foundation in 1913 does not fit the mold of the more contemporary physician manpower studies discussed later, it has probably exerted a greater influence on determining the supply of physicians than has any of its successors. It is worthwhile, therefore, to recall that Flexner proposed a substantial reduction in the number of the nation's medical schools, from 155 to 31, and to limit their total capacity to a graduating class of 3500 students. These reductions, Flexner believed, would still provide enough physicians to meet the nation's needs for at least two generations. State legislatures and others in health policy promptly endorsed many of Flexner's recommendations, with the result being that more than half the medical schools in existence at the time were subsequently closed.

Twenty years later, in 1933, two economists, Lee and Jones,[3] established what has become the classic needs-based approach to analyzing manpower for health care. This approach involved developing annual population expectancy rates of disease and injuries from which expert physicians made professional judgments on the number of medical services and the amount of time that would be required to diagnose and treat each illness. Based on their extensive data collection and analysis and using a 40-hour workweek as a baseline, Lee and Jones calculated that 165 000 physicians would be required to meet the nation's needs, or a ratio of 135 physicians per 100 000 population. To these investigators, a "shortage" of physicians was equal to the difference between the current physician-to-population ratio and the ratio calculated using their needs-based method.

Although there were other reports and studies during the next three decades, perhaps the most significant was the 1959 Report of the Surgeon General's Consultant Group on Medical Education.[4] The upshot of this report was its attempt to establish a normative benchmark for assessing future re-

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From the University of Michigan Medical Center, Ann Arbor. Dr Buerhaus is now at the University of Iowa, Iowa City.

Presented in part at the Clinical Congress of the American College of Surgeons, Atlanta, Ga, October 17, 1989. Portions of this report were also presented at the annual meeting of the Kentucky Chapter of the American College of Surgeons, Lexington, April 27, 1990.

Reprint requests to the University of Michigan Medical Center, Medical Science I Bldg, 1301 Catherine St, Box 0608, Ann Arbor, MI 48109-0608 (Dr Zuidema).

quirements of physicians, and that benchmark was to equal 140 physicians per 100 000 population, which incidentally was the ratio that existed in 1959.

The Study of Surgical Services for the United States, better known as SOSSUS, was the next important effort to analyze physician manpower needs.[5] Conducted between 1970 and 1975, SOSSUS was a comprehensive study sponsored by the American College of Surgeons and the American Surgical Association. Its purpose was to collect and synthesize data on all phases of surgical care, including the following: surgical manpower; organization, provision, and financing of surgical services; interprofessional relations; quality of surgical care; legal and ethical issues; surgical research; and implications for surgery and government relations.

With respect to its surgical manpower analysis, the study was composed of four separate but related studies. One study collected data on the number and rate of surgical operations performed within four geographic areas of the United States during 1970, and another study collected and analyzed data on the distribution of board-certified surgeons throughout the country. Additionally, two studies were conducted in which separate surveys of practicing surgeons and residents were administered to collect data on work patterns, number of operations performed, biographic characteristics, income, and how professional time was used. Data were also collected on the number of medical school graduates expected to enter and complete surgical residency programs, the number of foreign medical graduates entering surgical residency programs, the number of board-certified surgeons, the number of deaths of physicians, retirement rates of physicians, and the growth rate of the US population.

The results of these separate studies were brought together to formulate projections on the number of board-certified surgeons per 100 000 population for the 10 surgical specialties that existed at the time. The Study of Surgical Services for the United States concluded that 54 000, or a ratio of 24 *board-qualified* and *board-certified* specialists per 100 000 population, was reasonable. However, if the number of *non-board-certified* surgical practitioners was included in the count, then the total number of physicians performing surgical operations was thought to be excessive. Finally, SOSSUS recommended a reduction in the number of surgical residents and board certification rates to between 1600 and 2000 per year through the 1980s.

The next major physician manpower study was conducted by the Graduate Medical Education National Advisory Committee (GMENAC).[6] The model GMENAC used to calculate the future *supply* of physicians involved four components. The first used 1978 as the baseline and estimated that there were 375 000 full-time–equivalent, actively practicing physicians. This number was then adjusted to account for expected deaths, disabilities, and retirements, which led to a projection of the number of physicians who will be *actively* practicing in the next two decades. The second component of GMENAC's supply model estimated the number of graduates from US medical schools, students who were expected to transfer from foreign medical schools to US medical schools, and those expected to enter practice in the United States after completing residency requirements.

The third component projected the number of future graduates of foreign medical schools who were expected to enter practice in this country after completing their residency training. The final supply-side component attempted to account for the provision of medical care contributed by residents in training. The Graduate Medical Education National Advisory Committee concluded that, on average, each resident was equivalent to 35% of one full-time, active physician. The results of these four supply-side components were combined to formulate projections on the numbers of physicians expected to be actively practicing in 1990 and in 2000.

Table 1.—Graduate Medical Education National Advisory Committee Physician Manpower Estimates*

Year	Supply	Requirements	Oversupply
1990	535 750	466 000	69 750
2000	642 950	498 250	144 700

*Data from Graduate Medical Education National Advisory Committee.[6]

The method used by GMENAC to determine future *requirements* for physicians was more complex and relied heavily on subjective judgments. First, an expert panel of physicians determined the ideal norms of medical care for all diagnoses of the *International Classification of Diseases, Hospital Adaptation.* Next, a "modeling panel" examined each of the norms of care and made further revisions in three areas: eliminating overlaps in which two or more specialties dealt with the same disease or condition; superimposing economic, social, and behavioral constraints to make more realistic the attainment of the level of services for each disease or condition; and considering how other health care professionals could meet physician requirements for each specialty. The effect of these adjustments was to make GMENAC's recommendations on physician requirements reflect a middle position between what was truly needed and what was reasonably achievable by 1990 and by 2000. Table 1 shows GMENAC's projections of the supply of and requirements for physicians.

The Graduate Medical Education National Advisory Committee's methods and projections have not avoided criticism. As Harris[7] has commented, the number of published criticisms of the GMENAC report is an indication of the influence it has had on public policy. The subjectivity involved in making judgments about medical care needs has probably been the most controversial area, but GMENAC has also been criticized for not adequately anticipating the number of women entering medicine; failing to foresee the liability crisis that has caused many physicians to reduce the scope of their practice or retire early; ignoring the growth in health maintenance organizations (HMOs) and the resultant changes in the productivity of physicians working in managed-care settings; and not anticipating the onset of acquired immunodeficiency syndrome or how Alzheimer's disease could change requirements for physicians. These shortcomings are mentioned here, not as an attack on GMENAC, but simply to illustrate how quickly events change, and to point out that much of the accuracy and practical value of manpower projections depend on the scope and validity of underlying assumptions and data.

PHYSICIAN MANPOWER STUDIES SINCE GMENAC

In one way or another most of the physician manpower studies reported since the GMENAC study have attempted to address the aforementioned criticisms, update assumptions, and use more current data. For example, the major focus of Tarlov's[8] study was on analyzing how growth of the population enrolled in HMOs would reduce requirements for physicians. After first updating several factors affecting the supply of physicians, Tarlov formulated two scenarios concerning the proportion of the population that might be covered by HMOs in the future. The first scenario used a baseline ratio of 120 physicians required per 100 000 enrollees in HMOs, and assumed that 120 million people (ie, approximately 44% of the population) would be enrolled in HMOs in the year 2000 The second scenario assumed that 60 million people would be enrolled in HMOs. In either case, Tarlov concluded that the growth in HMO enrollees, together with the effect of regulations and practice arrangements that are being implemented to decrease utilization of medical care, will result in a steady decline in the demand for physicians' time in the years ahead.

The next set of physician manpower projections was published by the federal government's Bureau of Health Professions (BHPr).[9] On the *supply* side the BHPr updated projections on the number of foreign medical graduates, medical school enrollments, and medical student transferees who would be entering medical practice. These modifications led to a prediction of 708 000 and 820 810 actively practicing physicians in the years 2000 and 2020, respectively. Projections of the total number of physicians required were based on assumptions concerning changes in the population, medical care prices, the extent of the population covered by health insurance, and a variety of other nonprice factors. A requirement of 637 000 physicians was projected for the year 2000, and 758 500 in 2020. When compared with its estimates of physician supply, the BHPr concluded that a surplus of 71 600 physicians will exist at the end of this decade and will decline only to 62 310 by the year 2020.

About the time that the BHPr's projections were published, Jacobsen and Rimm[10] reported the results of an analysis in which certain GMENAC supply-side factors were reassessed. These factors concerned enrollment declines in US medical schools, increases in the number of female physicians, and changes in the productivity of physicians. After making adjustments to each of these determinants, the supply of physicians in the year 2000 was projected to be 537 000. Comparing this prediction with GMENAC's estimated need of 498 000 physicians, an oversupply of 39 000 physicians was projected. Furthermore, noting that one of GMENAC's recommendations called for not allowing future graduates of foreign medical schools to practice in the United States, Jacobsen and Rimm estimated that had this recommendation been implemented, the projected surplus of full-time physicians would only be 6000 by the year 2000.

In the latter part of the 1980s, the American Medical Association (AMA) Center for Health Policy Research also conducted a study on physician manpower.[11,12] The AMA's supply-side projections were based on different assumptions than BHPr's model concerning the number of US medical graduates, the number of foreign medical graduates, the number of allopathic physicians, attrition rates, and retirement rates for men and women in the base year 1986. Although its supply estimates were lower than the BHPrs, the AMA nevertheless projected a 24% increase in the supply of physicians between 1985 and the year 2000.

Unlike the BHPr's model projecting *requirements* for physicians, which assumed variation in utilization by age, race, sex, per capita income, and price of medical care, the AMA model assumed that most of these variables would remain relatively constant. As a result, it estimated a 14.5% growth in utilization between 1985 and the year 2000, whereas the BHPr's estimate was 19.1%. Although the AMA acknowledges that supply will grow faster than demand, it makes explicit its view that this does not necessarily imply a surplus of physicians. The authors of the study write:

> Concepts of surplus or shortage as used in the health manpower literature are essentially normative comparisons. Our analysis uses current utilization patterns as a base of comparison. These patterns do not represent a normative standard because not all segments of society utilize health services "appropriately."[11(p3)]

The next-to-last study reported in the research literature provides a different scenario than the studies reviewed thus far. Schwartz and colleagues[13] used BHPr's supply-side estimates but made additional adjustments to account for the number of physicians primarily engaged in teaching, research, and administration or other activities *not* directly involved with providing patient care. They also made refinements in estimates of the number of physicians who are women, and made adjustments to reflect fewer clinical services provided by house officers due to shorter workweeks, which these investigators believe will become the norm in the 1990s. The effect of these adjustments was to reduce substantially the BHPr's projection of the supply of active physicians from 708 000 to 585 000 in the year 2000.

Table 2.—Estimating the Supply and Requirements for Physician Manpower

	Year 2000 Projections		
Source, y*	Supply	Requirements	Excess (Deficit)
SOSSUS,[5] 1970-1975 If only board-certified or qualified surgeons are counted	. . .	. . .	Reasonable
If all others performing surgery are counted	. . .	. . .	Excessive
GMENAC,[6] 1980	642 950	498 250	144 700
Bureau of Health Professions,[9] 1986	708 600	637 000	71 600
Jacobsen & Rimm,[10] 1987	537 000	498 000	39 000
American Medical Association,[11,12] 1988	633 200 +24%	+14.5%	Normative judgments
Schwartz et al,[13] 1988	585 000	592 000	(7000)

*SOSSUS indicates the Study of Surgical Services for the United States; GMENAC, Graduate Medical Education National Advisory Committee.

On the demand side, Schwartz and colleagues[13] anticipated that advances in technology, rapid growth in the number of people with acquired immunodeficiency syndrome, aging of the population, increasing health insurance coverage, and gains in real personal income will combine to increase the demand for medical care between now and 2000. And, as in Tarlov's study,[8] several assumptions were made about the growth of competitive medical plans and their negative effect on the demand for physicians. Taken together, the above factors resulted in an estimated demand of 592 000 physicians in 2000. When compared with the supply prediction of 585 000, Schwartz and colleagues concluded that there will be a deficit of only 7000 physicians in 2000.

Finally, Schwartz and Mendelson[14] used economic theory to guide their analysis of data on hours of patient care provided by physicians, number of patient visits, and real physician income between 1982 and 1987. They argued that if the market for physician services was characterized by an excess supply, one would expect to observe a decrease in work loads and physician incomes. But because their analysis showed that hours of patient care had *risen* by 21.3% and physician incomes by 33.9% during the study period, demand must be increasing faster than supply. To bolster this claim, the investigators cited two recent surveys conducted by a physician recruitment organization, which found that both hospitals and medical groups were actively recruiting additional physicians.

The physician manpower projections made by these studies are summarized in Table 2. Although there is considerable disagreement in the size of the excess, most of the projections support GMENAC's prediction of an oversupply. Additional-

Table 3.—Projected and Actual Supply of Surgical Residents[15]

Surgical Residents' Specialty	American College of Surgeons Count, 1988/1990	GMENAC* Projections for 1990	% Change to Reach GMENAC 1990 Projection
General surgery	7982	9200	12.8
Pediatrics	35	. . .†	. . .†
Vascular	92	. . .†	. . .†
Colorectal	49	. . .†	. . .†
Neurologic	714	700	. . .‡
Obstetrics/ gynecology	4578	6200	35.4
Ophthalmology	1552	2600	67.5
Otolaryngology	1069	1400	31.0
Plastic	426	600	41.2
Thoracic	289	450	55.7
Urology	936	1600	70.9

*GMENAC indicates Graduate Medical Education National Advisory Committee.

†GMENAC's counts within general surgery included pediatric surgery, vascular surgery, and colorectal surgery. The American College of Surgeons' counts of these three specialties were included within general surgery to determine the required growth rate.

‡Has exceeded GMENAC's 1990 projection.

ly, the studies illustrate the different approaches, variables, and data sources that were used and underscore the sensitivity of projections to underlying assumptions. Therefore, it is not unreasonable to suggest that one should avoid expecting physician manpower studies to produce estimates that exactly match the number of physicians who will either *actually* be available or actually be required in future years. This point is made abundantly clear in Table 3, which shows a comparison of GMENAC's projections of surgical residents with the actual number of residents counted by the American College of Surgeons.[15] Although GMENAC was the most complicated and expensive of all manpower studies, nevertheless, with the exception of neurologic surgery, the actual number of residents in every surgical specialty is substantially below the number projected for 1990.

COGME'S PHYSICIAN MANPOWER STUDY

As noted earlier, COGME's Subcommittee on Physician Manpower is now conducting a study to fulfill the congressional requirement to produce a report in 1991 that will provide an estimate of the adequacy of physician supply for the next two decades. The study is designed to update GMENAC's needs-based model for estimating requirements for physicians in six physician specialties that were determined by the subcommittee to be under substantial stress. The specialties include family practice, general pediatrics, obstetrics/gynecology, general internal medicine, general surgery, and general and child psychiatry. In addition to quantitatively revising GMENAC's needs-based projections of GMENAC and extending them through the year 2010, COGME's supply projections will be based on the BHPr's projections through the year 2010. These projections will be adjusted to incorporate osteopathic supply and other modifications as deemed appropriate. There will also be a qualitative assessment of how various economic, social, and behavioral constraints may affect the future supply of and requirements for physicians.

The study will be managed for COGME by Abt Associates Inc, a Boston-based consulting firm, and led by coproject directors Gary Gaumer and William Mauder. They have met with representatives from each of the six specialties to elicit their input on the methodologic approach, relevant issues, and appropriate databases that should be used in the study. An advisory group has also been developed to assist the study directors and consists of approximately 30 members from the six physician specialty organizations, other specialties, and representatives from other health professions. With assistance from the advisory group, the study directors and representatives from the six specialties have begun to implement an analytic plan for reexamining the GMENAC's needs-based projections. This plan incorporates the following: (1) the methods for revising needs projections to the year 2010; (2) a determination of how and which morbidities and morbidity-related estimates will be revised or added (eg, acquired immunodeficiency syndrome); and (3) a determination of how other GMENAC modeling components will be revised to incorporate other changes (eg, the effects of shifts of inpatient care to outpatient settings or the effects of new technology). The revision of the needs-based methods and use of more recent data will culminate in the development of projections of *need* for the six specialties for the years 1990, 2000, and 2010.

To project the supply of physicians, the latest projections from the Bureau of Health Professions will be used. Osteopathic specialty supply for the six specialties will be factored into these projections, as will certain of the bureau's supply-side assumptions. These adjustments will include some of the factors described earlier, including, for example, the less than full-time–equivalent contributions of residents to patient care, the number of female physicians, changes in work productivity, and the geographic distribution of specialists.

The study will also provide an assessment of the effect that various economic, social, and behavioral constraints may have on the conclusions of oversupply or undersupply or on the relationship between the supply and need for physicians. Among others, these constraints will include issues concerning access to care; the problems of the underserved population, including minority, rural, and inner-city concerns; the effects of malpractice on retirement, access to care, and the future supply of obstetricians/gynecologists; changes in health insurance coverage among the population; differing standards of medical care by region of the country; effects of organizational structure on patterns of care and illness management; impact of diagnosis related groups and the resource-based relative value scale payment system; changes in resident work hours; and the impact of minorities on medical school enrollments, graduate medical education, and the physician manpower pool.

COMMENT

It is important to realize that in contrast to the generously funded GMENAC study, COGME's Subcommittee on Physician Manpower is confronted with substantial budget constraints. It is also obliged to complete the study in time to be included in COGME's overall report in 1991. These limitations have necessitated difficult choices concerning the number of specialties that could be studied and the degree to which all assumptions could be modeled quantitatively and incorporated into the analysis. To extend the breadth of the study, all the specialties have been invited to participate, although, of necessity, that participation has had to be at their own expense.

The COGME study is well under way, and there will be opportunities for all interested parties to review results, recommend changes, and otherwise participate in the process of making the study as valuable and useful as possible to all those who are concerned with making informed decisions on the nation's supply of physicians.

It is important to recognize, however, that there are certain limitations that are inherent in any needs-based manpower study. For example, a needs-based study deals with the issue on a national basis, and as such a series of very general assumptions are made. This type of study assumes an ideal, uniform distribution of both population needs and physician access. It is also predicated on a stable health care provision system and uniform ability to pay for health services. To accommodate these deficiencies, a number of important assumptions must be made, and these introduce possible errors in interpretation. We found this to be true with GMENAC and we can expect there to be many of the same kind of limitations with COGME.

This should not be used as a reason to negate or downplay manpower studies, but in fairness we should set the stage for COGME's study by acknowledging these limitations. This is especially true as we see our present health care system coming under increasing fire over issues of problems of access; the large number of underserved or underinsured, liability costs and unnecessary care related to defensive medicine; and costs of health care as part of our gross national product. We have a strong sense today that our health care system is in transition, and changes here will have a profound effect on manpower issues. We must be prepared to monitor manpower projections as an important element in our provision system and be prepared to respond as change appears necessary.

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Surgical Anatomy Question

Q The ligament of Treitz should be properly termed the *suspensory muscle of the duodenum.* [True or False?]

A [True] "At or close to its jejunal end, the duodenum has attached to it a suspensory *muscle* called the Ligament of Treitz or the suspensory muscle of the duodenum and mesentery."[1]

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Heart Transplantation in Jehovah's Witnesses

An Initial Experience and Follow-up

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Michael S. Sweeney, MD; O. H. Frazier, MD

• More than 25 years of experience performing heart surgery on Jehovah's Witnesses has culminated in successful cardiac transplantation without administering blood products in five patients (mean age, 44.4 ± 8.3 years) of this faith. The use of blood-conserving methods, iron supplementation, bone marrow–sparing maintenance immunotherapy, and brisk postoperative diuresis has added to the efficacy of cardiac transplantation in these patients. No perioperative deaths occurred, and early follow-up studies have shown that these patients have not been more susceptible to higher graft rejection rates due to the lack of pretransplant blood transfusions. As more Jehovah's Witnesses undergo heart transplantation in the future, comparison with other recipients who allow pretransplant blood transfusions may lead to a better understanding of rejection immunobiology. We conclude that cardiac transplants may be safely offered to Jehovah's Witnesses without fear of a uniformly poor outcome.

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In the 25 years since the Texas Heart Institute, Houston, first reported successful cardiac surgery in Jehovah's Witnesses,[1] many advances have been made to promote the safety and reliability of operations without the use of blood or blood component transfusions.[2-7] Although more Jehovah's Witnesses are undergoing low-risk cardiac operations with successful results, surgeons are generally reluctant to perform major cardiac operations in these patients.[8] We believe that special consideration to surgical detail, further development of asanguineous cardiopulmonary bypass techniques, and improved methods of perioperative management can result in a successful outcome at tolerable risk levels for this group of patients.

In 1986, Corno et al[9] reported the first successful cardiac transplant operation in a Jehovah's Witness. In 1988, we reported our first successful experience with heart transplantation in a Jehovah's Witness[10]; since then, four more have undergone transplants at the Texas Heart Institute. Our experience shows that cardiac transplantation in Jehovah's Witnesses can be expected to provide an outcome similar to that of any other subset of transplant recipients.

PATIENTS AND METHODS

Between October 1987 and July 1989, five patients of the Jehovah's Witness faith with end-stage cardiomyopathy underwent orthotopic cardiac transplantation at the Texas Heart Institute. All the patients were men, aged 44.4 ± 8.3 years (mean ± SD [Table 1]). None had undergone previous cardiac operations. Idiopathic cardiomyopathy was the indication for transplantation in all but one patient, who may have had a postviral cardiomyopathy. All patients refused to allow the use of blood or blood components, although one did allow reinfusion of shed mediastinal output from the bypass circuit. Other than their refusal of blood component therapy, patients had no other contraindications to transplantation.

Preoperative Evaluation

Preoperative laboratory studies were limited to prevent unnecessary hemoglobin reduction. The mean hemoglobin level (± SD) of the patients was 137 ± 15 g/L (range, 114 to 158 g/L), and lipid levels were normal. The mean preoperative serum iron and reticulocyte counts were 11.6 ± 1.9 μmol/L and $26 \times 10^{-3} \pm 8 \times 10^{-3}$, respectively. Serologic studies revealed that all five patients had been exposed to cytomegalovirus and herpes viruses, but not to hepatitis or human immunodeficiency viruses. All patients underwent cardiac catheterization procedures that revealed a mean ejection fraction of 17.4% ± 3.7% and a mean cardiac output of 3.7 ± 1.0 L/min.

Donor Selection

The donors included four men and one woman (mean age, 32.4 years), all of whom had body sizes and weights within 5% of their respective recipients. The mean ischemic time was 104.8 ± 51.6 minutes (range, 58 to 184 minutes). Two of the five patients received donor hearts obtained through long-distance procurement.

Perioperative Management and Operative Techniques

Immunosuppression was induced preoperatively with azathioprine (4 mg/kg of body weight) administered intravenously 4 to 6 hours prior to transplantation. In addition to receiving azathioprine preoperatively, one patient received 5 mg/d of muromonab-CD3 (Orthoclone OKT3; Ortho Pharmaceutical Corp, Raritan, NJ) administered intravenously for 7 days to complete induction of immunosuppression because he developed oliguria in the immediate postoperative period; when his renal function improved, he continued receiving the same baseline therapy as the other patients. To reduce hemodilution, only

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Table 1.—Patient Demographics

Age, y	Diagnosis	Ejection Fraction, %	Preoperative Hemoglobin Level, g/L	Hemoglobin Level at Discharge, g/L	Total Estimated Blood Loss, mL	Length of Hospitalization, d
46	Idiopathic cardiomyopathy	11	158	99	1765	13
53	Idiopathic cardiomyopathy	17	144	116	1350	30
45	Idiopathic cardiomyopathy	20	141	96	800	8
43	Viral infection	22	129	99	1575	13
35	Idiopathic cardiomyopathy	17	114	94	1000	26
Mean ± SD 44.4 ± 8.3	. . .	17.4 ± 3.7	137 ± 15	101 ± 8	1298 ± 365.2	18 ± 8.5

small amounts (mean, 1720 mL) of nonhemic crystalloid prime were used during cardiopulmonary bypass; no pulmonary artery catheters were used. To further limit the dilutional effects of the prime solution, shorter reduced-caliber extracorporeal tubing was used. No other deviations from our routine orthotopic transplantation protocol were necessary in any patient.

Postoperative Management

In the immediate postoperative period, the patients were given judicious volume expansion (hetastarch and lactated Ringer's solution) to maintain euvolia, and appropriate procoagulant therapy (eg, phytonadione or protamine sulfate) when necessary to enhance hemostasis. To further limit blood loss, laboratory studies were kept to a minimum. Pediatric phlebotomy tubes were used when possible. From postoperative day 2 through day 5, patients received adjusted doses of mannitol and furosemide to promote diuresis. Chest tubes were removed as soon as drainage ceased, usually by the third postoperative day. Autotransfusion of mediastinal output was used in only one patient. Intravenous iron dextran therapy (2 mL/d) was begun in the immediate postoperative period and continued until the patients resumed eating, at which time administration of oral iron supplements (325 mg every 8 hours) was started.

Immunosuppressive Management

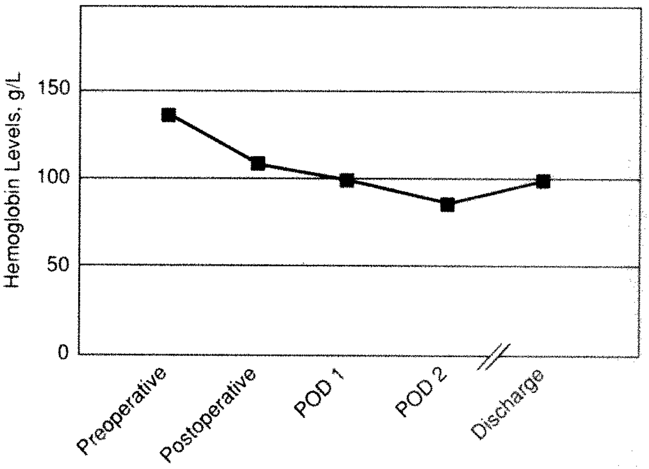
The immunosuppressive regimen consisted of administering graduated doses of cyclosporine intravenously, beginning with 2 mg/kg per day 12 hours postoperatively, and increasing the dosage to 4 mg/kg per day by the third postoperative day. Oral cyclosporine therapy (10 mg/kg per day) was begun when the patients resumed their diets and was quickly increased to a final dosage of 14 mg/kg per day by postoperative day 7 to day 10. Tapered doses of glucocorticoids were started with an intraoperative dose of 500 mg of methylprednisolone administered intravenously, followed by 125 mg every 8 hours for the next 24 hours.

Thereafter, cyclosporine doses were adjusted using whole blood techniques to maintain a trough level of 500 to 700 ng/mL (CYCLO-Trac SP^{125}/RIA Kit, Incstar Corp, Stillwater, Minn), and the corticosteroid dosages (prednisone) were tapered to oral maintenance doses (5 to 10 mg/d). Azathioprine was not included in the maintenance regimen because of the potential for bone marrow suppression.

Endomyocardial biopsy specimens were obtained on a routine basis according to established protocol to determine the extent of allograft rejection.[11]

RESULTS

All five patients survived the cardiac transplant operation. At this writing, four patients were in good health with length of follow-up ranging from 3 to 24 months (Table 2). The mean ejection fraction was approximately 59% (range, 51% to 78%). Two patients who underwent cardiac catheterization at 1-year follow-up had no evidence of accelerated coronary atherosclerosis. One of these patients died 13 months after transplant, the only late death in this series, as a result of discontinuing immunosuppressive therapy without the knowledge of his family or physician. On autopsy, advanced rejection and moderate coronary atherosclerosis were found. Compliance among the remaining patients has been excellent.



Hemoglobin levels following cardiac transplantation. POD indicates postoperative day.

Operative Results

All patients received orthotopic cardiac transplants. The mean cardiopulmonary bypass time was 68.6 ± 14.9 minutes (range, 55 to 91 minutes). Intraoperative blood loss was kept to a minimum. No patients required reexploration for hemorrhage, and the mean amount of chest tube drainage was 1010 mL (range, 600 to 1475 mL). The one patient who agreed to reinfusion of mediastinal output received approximately 400 mL of shed blood. None of the patients suffered excessive hemorrhage, despite elevated prothrombin times in three patients, two of whom had been receiving either warfarin sodium (Coumadin) or aspirin therapy prior to surgery.

The lowest hemoglobin levels generally occurred within 72 hours of the operation (Figure); the mean level was 87 ± 5 g/L (range, 77 to 92 g/L). All patients had normal or near normal hemoglobin levels by the time of discharge (Table 1).

Postoperative complications were generally minor and responded to therapy. One patient suffered atelectasis and required bronchoscopy; one had transient bacteremia that resolved with intravenous antibiotic therapy; and one had both oral herpetic lesions, which resolved with intravenously administered acyclovir, and a mild pericardial effusion, which resolved with diuretic therapy. The mean length of hospitalization was 18 ± 8.5 days (range, 8 to 30 days).

Incidence of Rejection

Three patients experienced one rejection episode each. Two of the patients had grade 6 rejection episodes[11] that were considered moderate and that responded to increased doses of cyclosporine administered intravenously. One patient had a

Table 2.—Follow-up Data

Time After Operation, mo	No. of Rejection Episodes (Grade)	Ejection Fraction, %	Hemoglobin Level, g/L	Survived
13	0	55	132	No*
14	1 (6)	51	116	Yes
4.5	0	60	140	Yes
2.5	1 (6)	78	112	Yes
2	1 (9)	51	102	Yes

*Cause of death was noncompliance with immunosuppressive regimen.

grade 9 episode that was considered severe, and he required brief monitoring in the intensive care unit while receiving pulsed glucocorticoids and OKT3 monoclonal antibody therapy. His rejection episode resolved after 10 days of OKT3 therapy, and he was discharged from the hospital in good health on the 26th postoperative day.

COMMENT

Five Jehovah's Witness patients have undergone orthotopic cardiac transplantation at the Texas Heart Institute with excellent results. All operations were performed without the use of blood or blood component transfusions, and none of the patients suffered major postoperative complications. They had a low incidence of rejection, and two of the patients had no signs of accelerated graft atherosclerosis at 1-year follow-up. Only one patient died of causes unrelated to the operation (noncompliance with immunosuppressive therapy). The remaining patients have fully cooperated with the complex posttransplant protocol, which involves frequent endomyocardial biopsies, changes in immunosuppression, and outpatient clinic visits.

Several factors influenced the success of cardiac transplants in these patients. None had undergone prior cardiac surgery, which is currently considered a contraindication for heart transplantation in this population because of the risk of excessive postoperative hemorrhage. Improved blood salvage techniques, such as acceptable methods of autotransfusion of shed blood, conservative bypass measures (eg, limited amount of prime, reduced-caliber tubing, and short bypass times), and meticulous operative technique can all improve patient care and minimize complications.[5,8,12] Optimal timing of recipient operations reduces the total ischemic time and duration of cardiopulmonary bypass, thereby minimizing the potential for postoperative hemorrhage. In addition, the lower average age of our Jehovah's Witness patients and their otherwise good general health contributed to the low incidence of bleeding complications and the eventual successful outcomes. Limiting postoperative phlebotomy to only the essential laboratory studies and using pediatric phlebotomy tubes helped preserve hemoglobin levels. Finally, aggressive postoperative management was vital to maximize oxygen delivery to tissues, particularly if hemoglobin reserves were low.

Since transfusions in Jehovah's Witnesses are prohibited due to religious beliefs, efforts to prevent the effects of severe anemia and to optimize oxygen delivery warrant careful attention. Early iron therapy has been shown to be effective, even after acute blood loss.[13] Despite intravenous iron therapy, none of the patients in this series suffered anaphylaxis or iron toxicity. Additionally, forced diuresis with intravenous loop diuretics can artificially raise hemoglobin levels by eliminating excess extravascular body fluids obtained during extracorporeal bypass.

Other agents that appear to have potential for improving the safety of surgery without transfusions include perfluorocarbons, desmopressin acetate, aminocaproic acid, and recombinant erythropoietin. Some investigators[7] have advocated blood alternative compounds, such as the perfluorocarbons (Fluosol-DA 20%), for use in treating Jehovah's Witnesses. Desmopressin acetate, which primarily improves platelet function and increases the level of the vWF, has been shown to aid in the treatment of postoperative hemorrhage, and it was used successfully in one of our patients in this series.[14-17] Another alternative, aminocaproic acid, is a potent inhibitor of fibrinolysis.[18] Its principal effect is mediated by inhibition of plasminogen activator substances, and its lesser effect is accomplished through modulation of antiplasmin activity. In the future, a third alternative, recombinant erythropoietin, which is currently undergoing clinical trials, may prove to be beneficial. Erythropoietin has been shown to reduce transfusion requirements and to increase erythropoiesis in anemic patients undergoing chronic hemodialysis,[19] and this has implications for patients with chronic anemia and for those who refuse blood transfusions or have rare blood types that are difficult to crossmatch.[20]

As more Jehovah's Witnesses undergo cardiac transplantation without blood or blood component transfusions, comparing their results with patients who have previously received blood products may make it possible to further define the effects of blood transfusions on immune conditioning. Some investigators[15,21-26] believe that if patients undergoing transplantation have received one or more blood transfusions prior to the transplant operation, they are less likely to experience rejection and, perhaps, have a better graft survival rate. Although we have performed only five heart transplants in Jehovah's Witnesses, our early results indicate that they are not necessarily more susceptible to rejection episodes or to having poor graft function. The incidence of rejection has, in fact, been minimal, implying that other factors may also be responsible for immune conditioning.

Careful consideration must be given to the type of immunosuppressive therapy Jehovah's Witnesses receive. Some drugs, such as antilymphocyte globulin, may have restrictions against their use because of religious prohibitions. Others, like azathioprine, cyclophosphamide, and methotrexate, are known to have detrimental effects on hematopoiesis and are not recommended for maintenance immunosuppression. Although induction therapy in our patients has included low-dose azathioprine, its use was strictly avoided for maintenance therapy, especially since a regimen of cyclosporine and a steroid taper has yielded good results. For patients who experience renal failure, an effective alternative to cyclosporine is the OKT3 murine monoclonal antibody,[27] which we used successfully in one of our Jehovah's Witness patients until his renal function was restored.

CONCLUSION

Cardiac transplantation can be a viable therapeutic alternative for patients of the Jehovah's Witness faith who have end-stage cardiomyopathy, despite their refusal to accept blood transfusions. The five patients who underwent transplantation at our institution all survived the operative period. Moreover, they did not experience severe postoperative complications, have not had signs of advanced graft atherosclerosis, and have not been particularly susceptible to rejection episodes. Our experience shows that with careful patient selection, meticulous operative technique, effective iron therapy, judicious diuretic management, and proper immunosuppression, Jehovah's Witnesses can expect as beneficial an outcome as any other group of prospective cardiac transplant recipients.

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Invited Commentary

This report of successful cardiac transplantation in five patients whose religious convictions precluded their receiving blood products raises several interesting and important questions.

Does the use of scarce donor organs in the setting described represent effective resource utilization? Life-threatening hemorrhage due to a technical problem or to a coagulopathy associated with cardiopulmonary bypass, even in carefully selected patients, cannot always be predicted. Were a death to occur that could have been prevented by the administration of blood products, the net loss would be two lives, not one: the patient who actually died and the potential recipient who did not receive the donor organ. It is well known that there are far more potential recipients for donor hearts than there are donor organs available. Therefore, the possibility that a preventable death might occur makes such utilization of a scarce resource a societal as well as an individual concern.

The authors have, wisely in my opinion, limited their study to patients who had not had prior cardiac surgery or other known complicating factors. Blood drawing for laboratory tests was kept to a minimum, iron supplementation was begun in the early postoperative period, and diuretic therapy was used in all patients. A measurement of bleeding time might have proved useful in this group of patients, since this test, along with a measurement of the red blood cell volume (which was done in this study), were strong predictors of the need for postoperative transfusion in one recent report (*J Thorac Cardiovasc Surg.* 1989;98:492-497). Perhaps a lesson to be learned from the study by Burnett et al is that there is an opportunity to streamline the hospital course of virtually all cardiac surgery patients in an effort to simultaneously avoid the administration of blood products and to be more cost-effective in the delivery of high-quality health care.

Although the authors chose to avoid the use of azathioprine because of its bone marrow–suppressing properties, the antierythropoietic effects of this drug when given in the usual doses is minimal. Nonetheless, the use of an immunosuppressive regimen consisting of cyclosporine and steroids has been effective in some renal transplant programs, even though experience with this type of regimen in cardiac transplantation is meager. The only published trial of which I am aware compared a regimen consisting of pretransfusion/azathioprine/steroids with one of cyclosporine/steroids; no differences were found in the short-term survival in cardiac transplant recipients (*Circulation.* 1985;72[suppl II]:227).

This report documents that cardiac transplantation *can* be successfully done in patients without the use of blood or blood products, but there is no recommendation that the procedure should be offered to this or any particular group of patients regardless of their practices. It is most important that so long as the donor organ remains the limiting resource, each potential recipient be evaluated with respect to the appropriateness of his or her candidacy so that the maximum benefit for the most people is achieved.

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Ambulatory Cholecystectomy Without Disability

Walter P. Ledet, Jr, MD

• This is a presentation of 200 consecutive outpatient cholecystectomies performed during a 4-year period in a small community hospital. This technique is performed with minor modifications of the usual cholecystectomy procedure so that it could easily be performed by general surgeons throughout the United States. The procedure has resulted in a large reduction in the short- and long-term morbidity associated with cholecystectomy, and in savings of up to one fourth the cost of a routine inpatient cholecystectomy. This procedure allows the general surgeon to treat patients with cholecystectomies in the fashion to which the surgeon is accustomed and still markedly reduce the hospital stay. The morbidity from this procedure seems comparable with laser cholecystectomy. Ambulatory cholecystectomy as described here does not require any special training or equipment.

(*Arch Surg.* 1990;125:1434-1435)

Between April 1986 and February 1990, 200 consecutive cholecystectomies were performed on an outpatient basis at the West Calcasiu Cameron Hospital, Sulphur, La. Patients were selected for this procedure on the basis of their desire for and acceptance of ambulatory surgery. No patient was rejected solely because of age or weight. Patients were rejected for ambulatory cholecystectomy only on the basis of significant contraindicating medical problems.

Patients in this study ranged in age from 16 to 82 years, and in weight ranged from 52.3 to 127.3 kg. No patient required rehospitalization, and to date, there have been no wound infections, hernias, or any medical complications.

The major importance of this report is to indicate feasibility of ambulatory cholecystectomy and to note that aggressive postcholecystectomy care can markedly reduce patients' short- and long-term morbidity.

AMBULATORY CHOLECYSTECTOMY WITHOUT DISABILITY

Cholecystectomy is the most common major general surgical procedure performed annually in the United States. It is currently estimated that approximately 500 000 cholecystectomies are performed each year in this country. Many articles have been published in which cholecystectomy discharge times were in the range of 1 to 3 days.[1,2] No accounts, however, have been published of attempts to perform this procedure as an outpatient procedure.

Many attempts have been made in the past to reduce the incidence of cholecystectomy by medical management. Medical dissolution of gallstones has not been uniformly successful, and more recently, attempts are being made in Europe and in this country to remove gallstones by ultrasound lithotripsy.[3,4] In an effort to reduce the morbidity associated with cholecystectomy, a program of ambulatory cholecystectomy in a community hospital setting has been evolved. The short- and long-term morbidity are greatly reduced by this procedure.

METHODS

The diagnosis of gallbladder disease was made in the standard fashion, with either ultrasound or cholecystography, or in some cases a clinical diagnosis was made.[5,6] In the acute setting, ultrasonography was used almost extensively. The patients were admitted to the outpatient treatment facility on the morning of surgery, and 5% dextrose with lactated ringer solution was administered intravenously in the peripheral vein. The preoperative treatment consisted of (1) 5000 units of heparin sodium administered subcutaneously, (2) 2 g of ceftriaxone intravenously, (3) 0.3 mg of glycopyrrolate (Robinul) intravenously, (4) 5 mg oxycodone and 500 mg acetaminophen (Tylox, 2 tablets) by mouth, and (5) 30 mg of prochlorperazine maleate (Compazine spansule) by mouth.

The incision used was a right-upper-quadrant transverse abdominal skin crease incision, made in a skin crease in the upper abdomen and often just 1 cm above the umbilicus. The incision varied in length between 5 and 10 cm, depending on the age of the patient, the body habitus, and the necessity for a general abdominal exploration. Cholecystectomy was performed by the standard operative technique, with the following modifications. The incision made was a transverse abdominal incision made in the skin fold of the upper abdomen, which in female patients was often only 1 cm above the umbilicus. The incision was made for a distance of 5 to 7 cm depending on the patient's body size. In patients in whom an abdominal exploration was required, the incision was enlarged enough for the operator to insert a hand in the abdomen and completely explore it. A small blade (Balfour, Baxter Healthcare Corp, McGaw Park, Ill) and an upper abdominal hook (Incredible Hook) attached to an ether screen were used for upper abdominal retraction. Retractors (standard Dever or Harring-

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ton) were used as indicated. The cystic artery was initially identified and transected between hemoclips and the cystic duct was treated similarly if no cholangiogram was needed. The gallbladder was then removed from the liver bed by a combined antigrade and retrograde dissection. In some instances in which the gallbladder was distended and tense, bile was aspirated until the texture of the gallbladder was soft enough for removal without danger of rupture.

Common duct exploration may be performed without changing the incision, and in these cases, the common duct was closed primarily. These cases, however, were not added to this series and will not be discussed in this article.

Abdominal wound closure was carried out in layers without drainage. Prior to wound closure, the upper abdomen was irrigated with kanamycin sulfate and saline solution.[7] Each abdominal wound layer was then closed with running sutures of blue monofilament polybutester (Novafil) and each layer was injected with a solution of 0.25% bupivacaine hydrochloride (Marcaine) with epinephrine bitartrate. The rectus abdominus muscle was injected with a solution of 30 mg of long-acting dexamethasone sodium phosphate (Decadron) diluted in 20 mL of normal saline and 10 mL of 0.25% bupivacaine and epinephrine. Skin closure was completed with a running 5-0 nylon suture and an air-strip dressing was applied along with an elastic rib belt. The first 30 patients did not receive dexamethasone injections as described. It is my distinct impression that the patients have done considerably better since the use of intramuscular dexamethasone.

In the recovery room, the patient started receiving acetaminophen and prochlorperazine orally. Treatment with Tylox was continued as two tablets every 2 hours during the patient's hospital stay, which ranged between 3 and 10 hours. This was continued at home for 2 to 4 days, in gradual decreasing amounts according to the patient's tolerance. The prochlorperazine maleate was prescribed as one 15-mg spansule every 6 hours for the first 48 hours. Emphasis was placed on the prevention of pain and nausea, early exercise, and the return to normal activity.

After discharge, the patients were followed up by telephone two times a day for the first 5 or 6 days. The patients came to the office for suture removal in 7 days.

RESULTS

All patients admitted to this study were discharged between 3 and 10 hours after completion of the surgical procedure. Approximately 20% of the patients complained of nausea following discharge, and about 5% of these experienced some vomiting after they were discharged. There have been no cases of wound infection, hernia, thrombophlebitis, or pulmonary embolization.

Patients were given two pages of discharge instructions indicating the care and follow-up required as documented herein. It has been most rewarding to see patients resume their normal activity with some limitation the day following surgery, several of whom returned to executive jobs. Patients with sedentary jobs were able to return to regular work within 4 to 5 days. Patients who require heavy work were able to return by 21 days and sometimes sooner if allowed a light duty status by their employers.

Patients were encouraged to begin moderate physical activity immediately after surgery. They were asked to exercise to tolerance, but to stop as soon as they became tired, and rest as much as they required. Most patients could drive themselves to the office for suture removal at 7 days.

FINANCIAL DATA

Our community hospital developed an all-inclusive charge for ambulatory cholecystectomies at US $1500. This included not only the operating room, anesthesia, and recovery room charges, but also preoperative costs, costs of laboratory work, and roentgenograms. The average retrospected charge for an inpatient uncomplicated cholecystectomy was approximately US $3500. This modest charge made it possible for patients without insurance coverage to afford cholecystectomy in a private hospital setting. Some insurance carriers now provide 100% coverage for outpatient surgery. Some of our patients benefited from this also.

COMMENT

Over the past 3.5 years, 150 consecutive cholecystectomies were performed on an outpatient basis. Aggressive postoperative management made it possible for the patients to return to their routine activity within 7 to 10 days. This has been a very exciting but unexpected by-product of doing ambulatory cholecystectomy.

This procedure is seen to be effective not only in young patients but also in elderly and obese patients. It is applicable to most general surgical settings throughout the United States and could result in remarkable financial savings to the health care system in the United States. Patients are most willing to accept this type of procedure after it has been shown to be successful and accompanied by decreased morbidity and moderate financial benefits.

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Invited Commentary

New techniques and technology should afford substantial medical or financial advantages over the old techniques and technology to justify their clinical application. I suspect that the obsolescence of the time-proven standard cholecystectomy is not imminent. This technique of outpatient cholecystectomy as performed by Dr Ledet appears to offer distinct advantages. Because it is a technically demanding alternative to standard cholecystectomy, surgeons should defer its use until its value is confirmed by appropriately controlled clinical studies. Even if the technique is proven valuable, some of us will be left behind. Thoracic surgeons, who failed to retrain to master the technical vagaries of open heart surgery, were replaced by those who did retrain and by surgeons trained in centers proficient in these techniques. Unfortunately, there are currently no centers to train surgeons in this technique of outpatient cholecystectomy.

Surgeons attempting this technique (and also laparoscopic cholecystectomy) should do so with the goal of benefiting their patients. Their results should be critically monitored by their hospitals and colleagues, and should compare favorably with those that they obtain with the time-proven standard cholecystectomy.

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Postoperative Complications in Patients With Disabling Psychiatric Illnesses or Intellectual Handicaps

A Case-Controlled, Retrospective Analysis

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• The purpose of this study was to quantitate the operative risk and costs encountered in the surgical treatment of institutionalized patients. Operative complications and duration of hospitalization for 200 institutionalized patients were compared with those in a control group of patients matched for age, sex, and type of operation drawn from the general hospital population. Postoperative complications occurred in 53 (26.5%) of the patients in the study group compared with 15 (7.5%) of the patients in the control group. Elective laparotomy was followed by a complication in 48% of institutionalized patients compared with 11.6% of matched controls. Emergency celiotomy carried a 75% complication rate in the study group. Atelectasis and pneumonia accounted for 50% of the postoperative complications and occurred with greatest frequency following intra-abdominal procedures. The median hospital stay for all institutionalized patients was 3 days more than for matched controls. A strategy for postoperative treatment is presented, with particular emphasis on prevention of pulmonary complications.

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Until relatively recently, a limited number of medical centers provided the bulk of nonpsychiatric medical care for institutionalized patients with profoundly impaired cognitive function or chronic psychoses. Referral patterns were prompted by geographical considerations, contractual agreements, or legislative fiat. During the last decade, however, there has been a national trend to reduce the population of state hospitals. Patients have been discharged under the care of their families or have been transferred to so-called halfway houses. Many others have added to the urban homeless population. Thus, the medical and surgical care of patients with chronic psychiatric disorders and intellectual deficiencies has become a widespread responsibility. Indeed, many hospitals and health care providers now routinely provide medical care for patients with major mental illnesses or handicaps despite having only limited experience in managing medical and surgical problems in this population.

The purpose of the present study was to quantitate the operative risk and to evaluate the special requirements encountered in the surgical treatment of institutionalized patients. A cohort of 200 such patients cared for in a university hospital was compared with a similar group of patients matched for age, sex, and type of operation. Based on this experience, we formulated a strategy for the surgical treatment of intellectually impaired and psychotic patients. Implementation of this strategy may help to reduce the morbidity, mortality, and expense of surgical treatment for such patients within the general medical community. In any event, the results presented here will provide practitioners with meaningful guidelines for assessing operative risk when considering surgical therapy for patients with these problems.

PATIENTS AND METHODS

We reviewed the medical records of 207 patients who were transferred from four nearby state institutions and who underwent operations at the University of Massachusetts Medical Center, Worcester, from 1977 to 1988. In addition to usual demographic data, we collected information regarding psychiatric diagnosis, presence of severe seizure disorder, and degree of intellectual impairment. Mental retardation was scored as none, mild, moderate, severe, or not specified. For the purposes of this study, it was assumed that the psychiatric diagnosis was correct, even though, in many instances, patients had been institutionalized for decades with a diagnosis such as chronic schizophrenia.

We recorded the name of the most significant surgical operation and its International Classification of Diseases code (*ICD-9-CM*).[1]

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Table 1.—Influence of Type of Operation on Morbidity and Mortality

	No. (%) of Patients							
	Abdominal Wall (n=31)	Intra-abdominal (n=43)	Endoscopy and Minor Gynecologic and Genitourinary (n=43)	Feeding Jejunostomy or Gastrostomy (n=7)	Major Orthopedic and Neurosurgical (n=15)	Minor Orthopedic and Neurosurgical (n=10)	Cutaneous (n=45)	Major Superficial (n=6)
Complications, institutionalized patients (n=53)	4 (12.9)	24 (55.8)*	2 (4.6)	6 (85.7)*	6 (40)	0	7 (15.6)	4 (66.7)*
Complications, matched controls (n=15)	1 (3.2)	5 (11.6)	3 (6.9)	0	2 (13.3)	0	4 (8.9)	0
Deaths, institutionalized patients (n=8)	0	5 (11.6)	0	0	1 (6.7)	0	1 (14.3)	1 (16.7)

*$P<.05$ vs matched controls (Fischer's Exact Test).

The need for special treatment, such as medications, attendants, or restraints, was noted. A control group of patients without known psychiatric diagnoses or intellectual deficiencies was selected from the general hospital population. The control population was developed by matching the *ICD-9* code for the primary operation to the same or very similar procedure. Satisfactory matches were possible for 200 patients. The patients in the control group all underwent surgery during the same decade as the patients in the study group and were matched for age (±5 years) and sex. Except for these constraints, the patients in the control group were selected at random.

Fourteen institutionalized patients ranging in age from 6 to 30 years had placement of a feeding gastrostomy or jejunostomy tube (*ICD-9* 46.39). Because of the infrequency of this procedure in the usual hospital population, a match was possible for only seven of these patients; the remaining seven patients were excluded from the study. Morbidity and mortality of the seven patients who were included were similar to those of the seven who were excluded. All postoperative complications and causes of death were noted for both groups of patients.

A complication was defined as an unexpected outcome of an operative procedure or a postoperative event that delayed hospital discharge by at least 1 day. Thus, a minor wound problem that did not prolong hospital stay was not considered a complication. Complications were divided into nine categories: pulmonary, wound, cardiac, urinary tract, deep venous thrombosis and pulmonary embolus, small-bowel obstruction, vomiting or ileus, seizures, and gastrointestinal bleeding. Only the most significant postoperative adverse event was recorded for each patient, although many patients had more than one complication. Operations were divided into eight categories: intra-abdominal, abdominal wall, endoscopy and minor gynecologic and genitourinary, feeding jejunostomy or gastrostomy, major orthopedic and neurosurgical, minor orthopedic and neurosurgical, cutaneous, and major superficial procedures. Operative procedures were further categorized as being emergency or elective. Emergency operations were defined as procedures that good clinical judgment required be performed within 24 hours of admission. The dates of admission, operation, and discharge were recorded to allow between-group comparisons of duration of preoperative, postoperative, and total hospitalization.

Data were stored in a computer (Apple MacIntosh II, Apple Computer Inc, Cupertino, Calif) using a commercially available database program (File Maker II, Copyright Claris Corp, Mountain View, Calif). Statistical analyses were performed on a computer (Vectra ES/12, Hewlett-Packard Corp, Andover, Mass) using commercially available software (CSS, Statsoft, Tulsa, Okla). Some data are presented as means; other results that were not normally distributed are presented as medians and ranges. For continuous variables (eg, duration of hospitalization), comparisons between the study population and the matched controls were performed using the Mann-Whitney *U* test. Comparisons of incidence data were performed using the χ^2 test. The null hypothesis was rejected for $P<.05$.

RESULTS

There were 200 institutionalized patients matched by age, sex, and *ICD-9* code to a similar number of patients from the general hospital population. Since patients were matched by age (±5 years), there was a slight difference in the mean age between the institutionalized group (52.6 years) and the control group (52.7 years). In both groups, 61.5% of patients were male.

The overall morbidity and mortality were substantially greater among institutionalized patients. Postoperative complications occurred in 53 (26.5%) patients in the study group compared with 15 (7.5%) patients in the control group ($P<.0001$). There were eight postoperative deaths (4.0%) in the institutionalized group and no deaths in the control group ($P=.0043$).

The magnitude of the operation and whether it was an emergency procedure were important factors affecting the frequency of postoperative complications for institutionalized patients (Table 1). Intra-abdominal, feeding gastrostomy, and major superficial operations were associated with a significantly greater incidence of postoperative complications compared with the control group (Table 1). Laparotomy, the most frequently performed major operation, was followed by a complication in 55.8% of institutionalized patients compared with only 11.6% of matched controls ($P<.0001$). Not surprisingly, emergency celiotomy was associated with an even greater risk of postoperative complications (Table 2). Of 12 emergency intra-abdominal procedures performed on institutionalized patients, nine (75%) resulted in a postoperative complication. Five of eight postoperative deaths in the institutionalized group followed emergency laparotomy. In marked contrast, there was no morbidity following eight emergency laparotomies in the control group.

A high complication rate was noted for institutionalized patients who had placement of a feeding jejunostomy or gastrostomy tube (85.7%). Whereas institutionalized patients undergoing these procedures were typically chronically malnourished with marked skeletal deformities and a long history of vomiting and aspiration, the control patients were usually previously healthy victims of head or spinal cord trauma.

All patients in the study group had one or more of the following broad diagnoses as the primary reason for their institutionalization: mental retardation, chronic psychosis, or chronic seizure disorder; 102 patients had two of these diagnoses and eight had all three (Table 3). Of these three diagnoses, severe mental retardation had the strongest association with postoperative complications. Patients with only mild mental retardation had a postoperative complication rate of 26.4%, similar to the study group as a whole. In contrast, the rate of complications in patients with severe mental retardation was 50.1%. The rate of complications in patients with epilepsy or psychosis alone did not differ from the entire study group.

Table 2.—Influence of Emergency Operation on Morbidity and Mortality of Institutionalized Patients

Group	Abdominal Wall (n=31)	Intra-abdominal (n=43)	Endoscopy and Minor Gynecologic and Genitourinary (n=43)	Feeding Jejunostomy or Gastrostomy (n=7)	Major Orthopedic and Neurosurgical (n=15)	Minor Orthopedic and Neurosurgical (n=10)	Cutaneous (n=45)	Major Superficial (n=6)
Elective operation complications, institutionalized patients (n=43)	4/31	15/31	2/40	6/7	6/13	0/9	6/41	4/6
Emergency operation complications, institutionalized patients (n=10)	0/0	9/12	0/3	0/0	0/2	0/1	1/4	0/0
Elective operation complications, matched controls (n=15)	1/31	5/35	4/42	0/7	2/14	0/9	4/43	0/5
Emergency operation complications, matched controls (n=0)	0/0	0/8	0/1	0/0	0/1	0/1	0/2	0/1

Table 3.—Institutional Diagnosis, Morbidity, and Mortality

	No. (%) of Patients		
Diagnosis	Study Group (N=200)	Study Group Complications (n=53)	Study Group Deaths (n=8)
No mental retardation	47 (23.5)	14 (26.4)	3 (37.5)
Mild mental retardation	7 (3.5)	0	0
Severe mental retardation	85 (42.5)	27 (50.1)	3 (37.5)
Degree of mental retardation not specified	61 (30.5)	12 (22.6)	2 (50)
Epilepsy	74 (37.0)	24 (45.3)	4 (50)
Psychosis	63 (31.5)	20 (37.8)	4 (50)
Mental retardation and epilepsy	65 (32.5)	23 (43.4)	4 (50)
Mental retardation and psychosis	24 (12.0)	7 (13.2)	1 (12.5)
Epilepsy and psychosis	13 (6.5)	2 (3.8)	0
Mental retardation, psychosis, and epilepsy	8 (4.0)	2 (3.8)	0

Regional (ie, spinal, epidural, or nerve block) anesthesia is believed to be associated with fewer postoperative cardiac and respiratory complications than general anesthesia. It is noteworthy, therefore, that general anesthesia was used for a greater proportion of patients in the institutionalized group (83%) than in the control group (64.5%) ($P<.001$) (Table 4). Within the institutionalized group, 95% of the postoperative complications and 100% of the mortality occurred in patients who received general anesthesia. In the control group, only 67% of the complications occurred after general anesthesia was administered ($P<.0001$).

Atelectasis and pneumonia accounted for 50% of the postoperative complications among institutionalized patients and occurred more frequently than in matched controls ($P<.0001$) (Table 5). Other types of complications occurred with an equal or greater frequency among institutionalized patients, but the between-group differences were not significant (Table 5).

There were eight deaths following surgery, all of which occurred in the institutionalized group. Four patients were in a preterminal state when they entered the hospital: two underwent exploratory laparotomy and colon resection for perforated cecal carcinoma; another had a tracheostomy and gastrostomy for severe chronic obstructive pulmonary disease and died a few days later; and the fourth developed peritonitis and septic shock when tube feedings were instilled into the peritoneal cavity from a displaced gastrostomy tube. The remaining four patients underwent the following operative procedures: radical neck dissection for tonsillar carcinoma, open reduction and internal fixation of a fractured hip, cholecystectomy, and lysis of adhesions for a small-bowel obstruction. Each of the last four operations was followed by aspiration pneumonia, progressive respiratory insufficiency, and eventually death.

Institutionalized patients used more hospital resources both before and after surgery than did counterparts from the general hospital population (Table 6). The median total preoperative hospital stay for institutionalized patients was 3 days longer than for the matched controls. When analyzed according to the type of operation, the duration of hospitalization was found to be most prolonged for the subset of institutionalized patients undergoing intra-abdominal procedures. Median preoperative, postoperative, and total hospital stays for noninstitutionalized patients undergoing celiotomy were as follows: 1 day (range, 0 to 16 days), 7 days (range, 3 to 16 days), and 9 days (range, 4 to 30 days), respectively. The corresponding values for the study group were as follows: 2 days (range, 0 to 81 days), 10 days (range, 1 to 58 days), and 12 days (range, 1 to 8 days), respectively. The probability for between-group comparisons of preoperative, postoperative, and total hospital stays after laparotomy were $P=.0113$, $P=.0002$, and $P<.0001$, respectively.

COMMENT

Relatively few publications have addressed the special problems and risks posed by surgical treatment of institutionalized patients. Indeed, data are scarce regarding the incidence of postoperative complications in patients, whether institutionalized or not, with severe cognitive handicaps or chronic psychoses. Previous studies have focused on the difficulty of making an early diagnosis of unusual disorders, such as pica, volvulus of the sigmoid colon, and rectal prolapse.[2,3]

Table 4.—Anesthesia and Morbidity and Mortality

	No. of Patients					
Type of Anesthesia	Study Group Total (N=200)	Matched Controls Total (N=200)	Study Group Complications (n=53)	Matched Controls Complications (n=15)	Study Group Deaths (n=8)	*P**
Local	6	20	1	0	0	.0045
Spinal/epidural	27	48	2	5	0	.0071
Block	1	3	0	0	0	NS
General	166	129	50	10†	8‡	<.0001

*Comparisons between study and control groups. NS indicates not significant.
†$P<.0001$ for comparison of complications between study and control groups receiving general anesthesia.
‡$P=.0114$ for comparison of deaths between study and control groups receiving general anesthesia.

Table 5.—Comparison by Type of Complication*

	No. of Patients								
Group	Pulmonary	Wound	Cardiac	Urinary Tract	DVT/ PE	Ileus/ Vomiting	SBO	Seizures	GI Bleeding
Institutionalized patients	26†	9	2	7	1	3	3	1	2
Matched control patients	2	5	2	4	0	2	0	0	0

*DVT indicates deep venous thrombosis; PE, pulmonary embolism; SBO, small-bowel obstruction; and GI, gastrointestinal.
†$P<.0001$.

Table 6.—Comparison of Hospital Use

	Median (Range) No. of Days		
Hospital Stay	Study Group (N=200)	Matched Controls (N=200)	*P*
Preoperative	1 (0-81)	1 (0-39)	<.0001
Postoperative	5 (0-100)	3.5 (0-89)	.0214
Total	7 (0-115)	4 (0-90)	.0016

To our knowledge, the present study is the first to compare the incidence and types of complications in institutionalized patients with those in a matched control group of patients drawn from the general hospital population. Consequently, the incremental risk of surgery for institutionalized patients, although suspected to be greater than that for their noninstitutionalized counterparts, was heretofore unquantified.

In this study the rate of postoperative complications in the institutionalized group as a whole was 26.5%, or 3.5 times greater than that for the control group. The postoperative mortality rate in institutionalized patients was 4%; none of the control patients died after surgery.

Other authors also have observed a high surgical morbidity and mortality for institutionalized patients. In an early review, Frederick et al[4] noted a postoperative complication rate of 19% and a mortality rate of 2.8% following a wide variety of operative procedures on 211 mentally retarded patients. More recently, Meyn et al[5] reported a major complication rate of 16% and a minor complication rate of 46% following hip surgery on 104 institutionalized patients. Their 6-week postoperative mortality rate was 5.7%. By way of comparison, in a subset of 15 patients from the present series who underwent major orthopedic operations, the complication rate was 40% and the mortality rate was 6.7% (Table 1).

The most striking postoperative morbidity and mortality followed intra-abdominal operations. The complication rate following elective laparotomy was 48%, but rose to 75% for emergency procedures. The mortality rate following emergency celiotomy was 16.7% (Table 2). In a Canadian study, Voitk[3] noted a mortality rate of 14% among 25 institutionalized patients following operations for an acute abdomen. Voitk attributed the excessive morbidity to delays in diagnosis due to several factors, including patients' impaired ability to communicate; alterations in the response to pain; and the failure of clinicians to suspect an unusual diagnosis, such as intestinal perforation resulting from the ingestion of foreign bodies (pica).

Although delay in diagnosis may contribute to increased morbidity in this population, other factors must also be important since the complication rate following elective laparotomy in the present study was 48%. Pulmonary insufficiency, in one form or another, accounted for 50% of the complications following laparotomy (Table 5). In addition to the reduced functional residual capacity due to incisional pain, institutionalized patients were particularly susceptible to pulmonary insufficiency because of their limited ability to cooperate with respiratory therapy or to learn to use incentive spirometry effectively. In addition, the high incidence of gastroesophageal reflux among the institutionalized population may have contributed to aspiration in the postoperative period.[6-8]

One of the goals of the present study was to measure the incremental cost of surgical treatment for institutionalized patients. Hospital bills were not available for all patients for the duration of the study, and therefore could not be used as a basis for cost comparison. Although many factors determine cost, the only reliable data available for all patients in each group was the duration of hospitalization. Certainly, the number of hospital days bears a relationship to the total cost, as is emphasized by the present diagnosis related group system of reimbursement. The median duration of hospitalization for institutionalized patients was 3 days longer than for the matched control group (Table 6). However, when hospital stays were analyzed by the type of operation, we found that intra-abdominal procedures accounted for the greatest prolongation of hospital stay. For this subset of patients, the median postoperative stay was 3 days longer ($P = .0002$); the median total hospitalization also was 3 days longer ($P < .0001$).

Furthermore, the increased use of hospital resources was not simply a reflection of the increased frequency of complications in this group since the institutionalized patients undergoing uncomplicated laparotomy also had hospital stays averaging 4.7 days longer (data not shown). We speculate that one of the important factors prolonging hospitalization was a delay in the discharge of institutionalized patients because of the physicians' perception that such patients need to be more fully recovered before returning to an institutional environment. Since many state institutions have an infirmary in which patients from an acute care facility can complete their convalescence following an operation, improved communication between the surgeon and the institution probably could have effectively shortened the hospital stay in many instances.

Most plastic, gynecologic, genitourinary, orthopedic, and abdominal-wall procedures can be performed on institutionalized patients with a complication rate similar to that in the general population, particularly if the procedure can be performed under local or regional anesthesia (Table 1). However, major operations, especially emergency laparotomy, carry a substantial risk of pulmonary complications and a dramatically increased use of health care resources. As a result of our experience, we have developed a strategy designed to reduce the incidence of pulmonary morbidity for institutionalized patients.

We have found that the same techniques used to allay anxiety for pediatric surgical patients are also applicable to the institutionalized population. We recommend that patients be admitted 24 to 36 hours before surgery to allow familiarization with the new environment and to permit patients and staff to become acquainted. If patients will be going to an intensive care unit after surgery, it is helpful if they can visit the unit before the operation to meet the nurses who will care for them.

There appears to be a widespread perception that all institutionalized patients will be disruptive and difficult to treat and therefore should be isolated and sedated. In fact, this approach often increases their anxiety in response to the change in environment. The majority of patients have been in a stable social situation in their own facility and will be less disturbed if they are placed in semiprivate accomodations with an understanding roommate. Many of the tranquilizers in current institutional use have durations of action of several days or even weeks; the addition of short-acting sedatives is usually not necessary and may contribute to pulmonary morbidity. Kind words and patience often are more effective than more medication. When the patient's intellectual capacity permits, simplified respiratory training with incentive spirometry teaching should be performed.

It is important that the anesthesiologist perform a careful preoperative assessment of each patient so that he or she can gain the patient's confidence, select the most appropriate form of anesthesia, and judge the timing and dosage of sedation. In this study, general anesthesia was used more frequently than regional methods and may have contributed to atelectasis, retained secretions, and pulmonary complications. We suspected that the primary reason for selecting general anesthesia over regional anesthesia for institutionalized patients was the perception by the anesthesiologist that the patient would have limited ability to cooperate, or, in some cases, it was simply more convenient "to put the patient to sleep."

We believe that epidural anesthesia has the same advantages for the institutionalized patient as it does for the general population.[9] Epidural catheters can be left in place after surgery for analgesia, a tactic that may decrease the incidence of postoperative respiratory complications. Many institutionalized patients are surprisingly cooperative and tolerant of the minor discomforts associated with procedures performed under regional anesthesia.

The postoperative treatment of institutionalized patients poses a major challenge to the surgeon. If the patient can cooperate the usual methods of preventing atelectasis and expelling secretions, such as instruction in the use of incentive spirometry and forced deep breathing and coughing, will be effective means of prophylaxis. If the patient cannot cooperate, he or she will benefit from measures that require minimal patient cooperation, such as periodic nasotracheal suctioning to stimulate cough. The poorly cooperative patient may be apt to remove tubes or drains prematurely, contributing to his or her own morbidity.

We recommend that uncooperative patients be adequately sedated and ventilated with positive pressure until their lungs are clear and peristalsis has returned. At that time, patients should be rapidly weaned from the respirator, undergo removal of endotracheal and nasogastric tubes, and resume oral intake under close surveillance to prevent aspiration. These approaches require additional use of the intensive care unit but are effective in preventing atelectasis and aspiration, which are the two most important precursors of respiratory complications in this group of patients.

Nearly all authors on the subject of surgical treatment of institutionalized patients have emphasized the importance of early diagnosis of the acute abdomen as a means of decreasing morbidity. Although the value of early diagnosis cannot be disputed, it is probably not a realistic hope in light of the communication problems and chronically medicated state of many such patients. Therefore, reductions in operative morbidity and cost are most likely to occur as a result of increased understanding and anticipation of the special problems involved in the surgical care of institutionalized and similar patients.

We express our thanks to Roseann Lavin, RN, NP, and Francisco Melendez, MD, for their valuable assistance in collecting the data.

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Needle-Localized Mammographic Lesions

Results and Evolving Treatment Strategy

H. Richard Alexander, MD; Frank C. Candela, MD; D. David Dershaw, MD; David W. Kinne, MD

• From January 1981 to December 1987, 932 needle-localization breast biopsies were performed at our institution for mammographically detected abnormalities. We reviewed 531 needle-localization breast biopsy procedures performed during two periods (January 1981 to June 1984, n = 311; and January to August 1987, n = 220) to compare results and treatment patterns, and to determine the prevalence of the missed lesions. Mammographic abnormalities detected on routine screening accounted for a larger proportion of needle-localization breast biopsies in the later series (94 [30%] of 311 vs 94 [43%] of 220). However, the rate at which carcinoma was identified remained constant at 29% as did the percentage of cancers that were invasive (46% vs 51%). Overall, the rate of malignant diagnoses after needle-localization breast biopsy was lowest in asymptomatic women undergoing routine screening mammography (44 [24%] of 188) and significantly higher in women undergoing mammographic follow-up of the contralateral breast after treatment for breast cancer (28 [43%] of 65). There were seven missed lesions in 531 needle-localization breast biopsies, necessitating a second procedure in six and interval mammograms in one.

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Prior to the introduction of preoperative localization techniques for nonpalpable mammographic abnormalities, specimen roentgenography for calcifications was used in our institution to confirm that a biopsy had been performed on a suspicious lesion.[1,2] Using a variety of techniques, breast biopsy with preoperative localization has become well established as a procedure that is effective in the early diagnosis of clinically occult breast neoplasms.[3-14] Between 10% and 37% of needle-localization breast biopsies (NLBBs) result in a malignant diagnosis[5,6,15,16] and 40% to 60% of these are invasive.[12,13] While approximately 50% of women with clinically detected invasive cancers have axillary lymph node metastases, most series report only 10% to 30% involvement with clinically occult mammographically detected breast cancers.[4,8,10,11,13] Large epidemiologic studies have demonstrated the usefulness of screening mammography in the detection of clinically occult breast cancers and improving survival.[17-20]

Currently, the American Cancer Society recommends routine mammograms at regular intervals for all women over the age of 40 years. With the increase in screening mammographies performed using dedicated machines that pose minimal radiation risk (0.003 G per study), the frequency of NLBB has also increased significantly.[13] At our institution, NLBBs have increased more than 10-fold in the past 8 years. This translates into a significant expenditure of energy and coordination of time between surgeon, radiologist, and pathologist. Because of this increase, we compared 531 consecutive NLBBs performed during two periods to determine results, treatment patterns, and outcomes.

PATIENTS AND METHODS

From January 1981 to December 1987, 932 NLBBs for mammographically detected abnormalities were performed at Memorial Sloan-Kettering Cancer Center (New York, NY). A review of 531 consecutive operations performed from January 1981 to June 1984 (n = 311) and January to August 1986 (n = 220) was undertaken to compare results and treatment patterns, and determine the prevalence of missed lesions. All mammograms were interpreted and localizations were performed by two radiologists at our institution. Recommendation for biopsy was made on the basis of suspicious reoentgenographic findings as previously described[15] and include a mass with ill-defined borders or a stellate appearance; spiculated microcalcifications; or a combination of the two. All localizations were done using a mixture of 40% diatrizoate meglumine (Renografin) and 60% methylene blue dye injected adjacent to the suspicious area. Injections were given with a 20-gauge spinal needle and localization within 2 cm of the suspicious abnormality was accomplished in every case except one in which a hooked wire was inserted after the localization dye was discovered to be distant from the mammographic abnormality. A schematic illustration of the dye and its relationship to the abnormality and the localizing mammograms were sent with the patient to the operating room. All procedures were performed on an inpatient basis, almost always under a general anesthetic, by one of five surgeons from the Breast Surgery Service. At the discretion of the surgeon the specimen was sent for frozen section analysis and/or roentgenogram. Statistical analysis was performed by Fisher's Exact Test and considered significant at $P<.05$.

RESULTS

The frequency at which NLBBs were performed increased dramatically from 38 in 1981 to 569 in 1988 (Fig 1). Overall, 153 (29%) of 531 biopsies were carcinomas, of which 73 (48%) were

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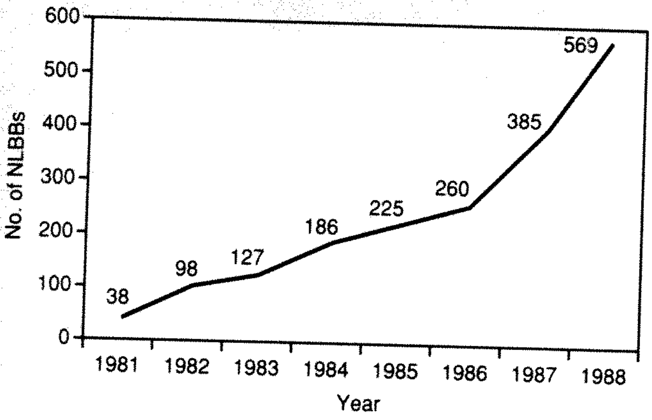

Fig 1.—Increasing frequency of needle-localization breast biopsies (NLBBs) performed at Memorial Sloan-Kettering Cancer Center, New York, NY, between 1981 and 1988.

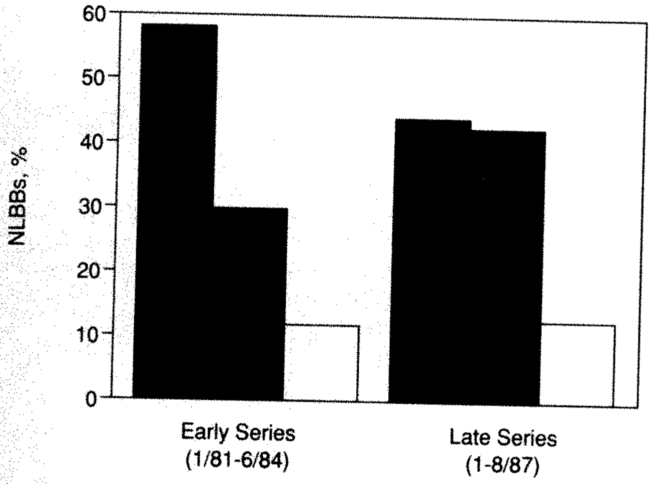

Fig 2.—Relative frequency of needle-localization breast biopsies (NLBBs) performed on abnormalities detected by mammogram obtained for clinical indications (closed bars), routine screening (dotted bars), or as follow-up in asymptomatic women previously treated for contralateral breast cancer (open bars). Proportion of NLBBs performed on abnormalities identified after routine screening has increased significantly ($P<.05$).

Table 1.—Malignant Diagnosis and Percent Invasive Cancer After Needle-Localization Breast Biopsy

Period	No. of Patients	Cancer, No. (%)	Invasive, No. (%)
1/81 to 6/84	311	90 (28.9)	41 (45.5)
1/87 to 8/87	220	63 (28.6)	32 (50.8)
Total	**531**	**153** (28.8)	**73** (47.6)

invasive (Table 1). Mammography was performed for clinical indications in 53% (pain, nipple discharge, mass, or family history; n=278); routine screening in 35% (n=188); or a history of contralateral breast cancer in 12% (n=65). The proportion of NLBBs performed for abnormalities detected on routine screening was greater in the later series, 43% vs 30% in the early series ($P<.01$, Fig 2). In spite of this, the rate at which carcinoma was identified remained constant at 29% as did the proportion of cancers that were invasive, 51% vs 46% (Table 1).

The rate of malignant diagnoses after NLBB was significantly higher in women undergoing mammography after previous treatment for contralateral breast cancer and was lowest in patients with abnormalities detected after routine screening, 43% vs 24% ($P<.05$, Table 2). More than 60% (17/28) of mammographically detected cancers were invasive in women with a history of previously treated contralateral breast carcinoma compared with 48% (73/153) overall. However, the size of the invasive tumors was not different between the groups. Overall, 50 (68%) of 73 invasive cancers were less than 1 cm and 68 (93%) were less than 2 cm. The incidence of lymph node metastases was low, occurring in 10 (14%) (Table 3). Treatment of invasive cancer was different between the two periods. Breast preservation therapy was more frequent in the later series, 10% vs 44% ($P<.001$, Fig 3).

There were seven missed lesions in six patients (1.3%) necessitating a second procedure in five cases, interval mammograms and physical examination in one, and a modified radical mastectomy in another who had malignant axillary adenopathy suspected of being a primary breast cancer (Table 4). Of the six missed lesions in which a tissue diagnosis was ultimately made, three were carcinomas. In five of the seven missed lesions, the surgeon found intraoperatively that the desired specimen was not excised when specimen roentgenograms failed to reveal the suspicious abnormality.

COMMENT

Despite the dramatic increase in the number of NLBBs being performed at our institution, the rate at which a malignant diagnosis is obtained has remained remarkably constant and compatible with other reports. Furthermore, this rate is similar to our initial experience, reported 15 years ago, with biopsy for suspicious microcalcifications and confirmed by specimen roentgenography.[2] The proportion of abnormalities detected on screening mammography has increased markedly and represents the primary factor in the increased number of NLBBs. Another report from our institution has described the risk of malignancy associated with various mammographic patterns.[15] The recommendation for biopsy based on these roentgenographic criteria has resulted in a stable rate of malignant diagnoses.

In women previously treated for breast cancer who had suspicious abnormalities detected on follow-up mammography, the rate of malignant diagnoses was significantly in-

Table 2.—Relationship Between Clinical History and Pathologic Features of Mammographically Detected Cancers

Indications for Mammogram	No. of Patients	Cancer, No. (%)	Invasive, No. (%)	Size of Invasive Cancers, cm*		
				<1	1.1-2	>2
Screening	188	44 (24)	18 (41)	13 (72)	3 (17)	2 (11)
Symptoms, PE or FH†	278	81 (29)	38 (47)	25 (66)	10 (26)	3 (8)
Previous breast carcinoma	65	28 (43)‡	17 (61)	12 (71)	5 (29)	0
Total	**531**	**153** (29)	**73** (48)	**50** (68)	**18** (25)	**5** (7)

*Size of tumor was measured on pathological examination.

†PE indicates abnormal physical examination and FH, positive family history.

‡$P<.01$ vs screening.

creased. This point emphasizes the importance of routine mammography in this high-risk group. One factor that may be responsible for this finding is that a patient previously treated for breast cancer has usually had at least a baseline or even multiple mammograms previously, against which indeterminate appearing lesions can be compared and observed over time. On the other hand, there may be reluctance on the part of the surgeon to follow up a mammographic abnormality in a woman with a history of breast cancer. In this group, the size of invasive tumors was comparable with the overall group. No invasive cancers in women with a history of contralateral breast cancer were greater than 2 cm.

In our experience the dye injection technique has proven to be very effective. Complications related to injection of the dye were minimal. Syncope, which has been described with the hooked-wire technique, was also experienced by a few of our patients. While some have expressed concern that the dye may diffuse into tissues prior to the time of biopsy,[16] we have not found this to occur. In fact, most dye injections are performed in the morning and several hours may have elapsed prior to the actual operation. In spite of this, the methylene blue remains localized in the area of injection. In large breasts with deep lesions, the dye has been difficult to find on rare occasions and in this situation the hooked-wire may have some advantage.

Seven attempts (in six patients) to find the lesion, despite apparently adequate preoperative localization, were unsuccessful. This untoward event has been reported by others with approximately the same incidence.[11,16] During our earlier experience, a specimen roentgenogram was obtained at the discretion of the operating surgeon. Currently, if a biopsy is being performed for microcalcifications, an intraoperative specimen roentgenogram is obtained. Occasionally, if the surgeon is confident that the area has been excised, only a frozen section analysis is performed. Six of our missed lesions were realized at the time of the original operation as specimen roentgenogram failed to reveal the suspicious area. Repeated mammogram and biopsy were performed in five cases. One patient refused another operation and opted for close interval evaluation. Another patient was known to have malignant adenopathy and underwent modified radical mastectomy after NLBB failed to identify the carcinoma. Three of the seven missed lesions were carcinomas, emphasizing the importance of confirming the biopsy with a specimen roentgenogram. If specimen roentgenography, clinical judgment, or a frozen section diagnosis of carcinoma shows that the desired tissue has been excised, then no further localization is considered necessary. An interval mammogram in 4 to 6 weeks is appropriate in those rare situations when there may be doubt that the suspicious area has been excised. Inflammatory changes and patient discomfort make mammograms done sooner than

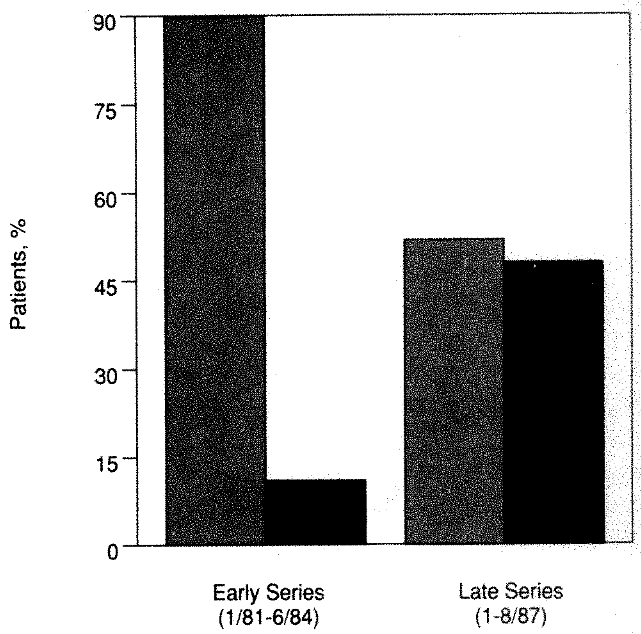

Fig 3.—The use of breast preservation (limited resection, axillary dissection, and radiation therapy) for mammographically detected invasive cancers has increased significantly (early series, four of 41; late series, 14 of 32; $P<.001$). Dotted bars represent modified radical mastectomies, and closed bars, breast preserving surgeries.

Table 3.—Tumor Size and Pathologic Stage of Occult Invasive Cancers, Early Late Series

	1981-1984, No. (%)	1987, No. (%)
Stage*		
I	35 (85.4)	28 (87.5)
II	6 (14.6)	3 (9.4)
III	0	1 (3.1)
Total	**41**	**32**
Tumor size, cm		
<0.5	10 (24)	5 (16)
0.5-1.0	18 (44)	17 (53)
1.1-2.0	10 (24)	8 (25)
>2	3 (8)	2 (6)

*Data from American Joint Commission on Cancer Staging and End Results Reporting. *Manual for Staging of Cancer.* 1983.

Table 4.—Outcomes of Seven Missed Lesions in 531 Needle-Localization Breast Biopsies*

Patient No.	Indication for Biopsy	Specimen Roentgenogram	Interval Mammogram	Second Specimen Roentgenogram	Pathologic Findings
1	Ca	No CA	3 d	Ca	FCD
2	Suspicious mass	Not done	2 wk	None†	IFDC
3	Suspicious mass	Not done	4 mo	None	None
4	Ca	No Ca	4 mo	Ca	IFDC
5	Ca	No Ca	2 d	Ca	DCIS
6‡	Ca	No Ca	5 mo	None	Normal
	Ca	No Ca			FCD

*Ca indicates calcifications; FCD, fibrocystic disease; IFDC, infiltrating ductal carcinoma; and DCIS, ductal carcinoma in situ.
†Patient underwent modified radical mastectomy.
‡A second attempt was made.

4 to 6 weeks difficult to interpret or perform. If the surgeon is certain that the suspicious area has not been excised, then repeated mammogram and localization is recommended as soon as clinically feasible. We have performed repeated localization and biopsy from 2 days to 2 weeks later.

The treatment of clinically occult invasive breast cancers appears to be appropriate with either modified radical mastectomy or breast preservation therapy. The trend toward more breast preservation therapy in the later series is a reflection of the current trend toward breast conservation therapy to all suitable candidates. In spite of consultation with a radiation therapist and a forthright discussion of the merits of each treatment, many patients with clinically occult invasive cancers still opt for mastectomy.

In conclusion, many more needle localization procedures are being performed at our institution primarily because of the abnormalities detected on routine screening mammograms. In spite of this, our rate of malignant diagnoses has remained stable. The dye injection technique has been very effective with no serious side effects. Intraoperative specimen roentgenography is the best way to confirm that a biopsy has been performed on the suspicious area and avoid the potentially serious consequences of a missed lesion. Patients previously treated for contralateral breast carcinoma have a significantly higher rate of malignant diagnoses than those undergoing NLBB after screening mammography.

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In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Cardiac Valve Prostheses at Autopsy

Linda B. Zeien, MD, Edward C. Klatt, MD

We describe the pathologic findings at autopsy in 96 persons who had undergone prosthetic heart valve implantation. The most common indication for implantation was rheumatic heart disease (58%), followed by infective endocarditis (22%). Cardiac failure led to death in two thirds of the cases, most often from infective endocarditis (18%) and congestive heart failure (13%). Failure of the prosthetic valve caused death in eight cases. There were 13 deaths intraoperatively or in the immediate postoperative period. Patients with mechanical prostheses survived longer than did those with bioprostheses. The most common prosthesis-related complication was thrombosis, found in 23% of mechanical valves and 11% of bioprostheses. Thrombosis led to death in only 4 cases. Thromboembolic phenomena led to nine deaths and were not related to anticoagulant therapy. These findings provide an approach to investigation, description, and diagnosis of prosthetic heart valves at autopsy (*Arch Pathol Lab Med.* 1990;114:933-937).

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Aerobic and Anaerobic Bacteriology of Wounds and Cutaneous Abscesses

Itzhak Brook, MD, MSc, Edith H. Frazier, MSc

• The aerobic and anaerobic microbiologic characteristics of 584 wounds and 676 skin or soft-tissue abscesses were studied and correlated with the infection site. In wounds, aerobic or facultative bacteria only were present in 223 specimens (38%), anaerobes only in 177 specimens (30%), and mixed flora in 184 specimens (32%). In total there were 1470 isolates, 558 aerobic and 912 anaerobic, an average of 2.5 isolates per wound (1.6 anaerobic and 0.9 aerobic isolates). In abscesses, aerobic or facultative bacteria were recovered in 177 specimens (26%), anaerobes only in 243 specimens (36%), and mixed flora in 256 specimens (38%). In total there were 1702 isolates, 602 aerobic and 1100 anaerobic, an average of 2.5 isolates per abscess. The highest rates of anaerobes in wounds were in the inguinal, buttocks, and trunk areas and in abscesses in the perirectal, external genitalia, neck, and inguinal areas. The predominant aerobic organisms were *Staphylococcus aureus* (363 isolates), group A streptococci (98 isolates), and *Escherichia coli* (97 isolates). The predominant anaerobic organisms were *Bacteroides* species (986 isolates), *Peptostreptococcus* species (559 isolates), *Clostridium* species (153 isolates), and *Fusobacterium* species (109 isolates). The predominance of certain isolates in certain anatomical sites was correlated with their distribution in the normal flora adjacent to the infected site. These data highlight the polymicrobial nature of wounds and cutaneous abscesses.

(*Arch Surg.* 1990;125:1445-1451)

Skin and soft-tissue infections are common in hospitalized patients. Knowledge of the common bacterial causes of these infections enables the selection of empiric antimicrobial therapy before the results of bacterial cultures are available.

The importance of aerobic and facultative bacteria, such as *Staphylococcus aureus*, in skin and soft-tissue infections is well established. However, only a few studies demonstrated the role of anaerobic bacteria in these infections.[1-4] Two of these reports evaluated the aerobic and anaerobic microbiologic characteristics of cutaneous abscesses in adults,[1,3] and one in children.[2] Only one report evaluated these organisms' role in wounds.[4] However, in three of these studies,[1,3,4] the species of most of the anaerobic organisms were not reported, and the role of aerobic and facultative strains other than *S aureus* and *Streptococcus* species was not evaluated.

This retrospective report described the experience over 14 years of a military hospital in the diagnosis of the aerobic and anaerobic bacterial etiology of wounds and skin and soft-tissue abscesses.

MATERIALS AND METHODS

Between June 1973 and June 1987, 584 specimens of wounds and 676 specimens of skin and soft-tissue abscesses that were submitted for the isolation of aerobic and anaerobic bacteria showed bacterial growth. Excluded from analysis were 29 specimens of wounds, because these wounds were treated with local antimicrobial therapy prior to sample collection. Specimens were processed by the clinical microbiology laboratories at the Naval Hospital in Bethesda, Md. Data regarding the administration of antimicrobial therapy prior to sample collection was available in 392 (67%) of 584 wounds and 431 (64%) of 676 abscesses. Systemic antimicrobial agents were used for 85 wounds (22%) and 92 abscesses (21%). These agents included β-lactamase–resistant penicillin (54 patients), erythromycin ethylsuccinate (31 patients), ampicillin sodium (28 patients), a cephalosporin (28 patients), penicillin G (18 patients), an aminoglycoside (15 patients), and clindamycin phosphate (four patients).

Of the 1260 patients from whom these specimens were obtained, 919 were males. Patients ranged in age between 2 weeks and 76 years (mean age, 39 years, 4 months).

Specimens were obtained from wounds or abscesses by direct needle aspiration of purulent contents into a syringe that was immediately sealed and transported to the laboratory within 30 minutes or by a swab that was dipped in the pus and introduced into anaerobic transport media (Port-A-Cul, BBL Microbiological Systems, Cockeysville, Md) and generally inoculated within 2 hours after collection.

For specimen collection through surgical drainage, the involved site was first scrubbed with providone-iodine. After local anesthesia with 1% lidocaine injection or ethyl chloride spray, pus was collected for culture by percutaneous aspiration of the abscess cavity or by swabbing-aspiration from the open cavity through a surgical incision.

Sheep blood (5%), chocolate, and MacConkey agar plates were inoculated for the isolation of aerobic organisms. The plates were incubated at 37°C aerobically (MacConkey agar) and under 5% carbon dioxide (blood and chocolate agar) and examined at 24 and 48 hours. For the isolation of anaerobes, specimens were plated onto prereduced vitamin K_1–enriched *Brucella* blood agar, anaerobic blood agar plates containing kanamycin and vancomycin, and anaerobic blood plates containing colistin and nalidixic acid, and then inoculated into enriched thioglycolate broth. The plated media were incubated in GasPak jars (BBL Microbiology Systems) and examined at 48, 96, and 120 hours. The thioglycolate broth was incubated for 14 days. Anaerobes were identified by techniques previously described.[5,6] Aerobic bacteria were identified using conventional methods.[7] The data were organized according to anatomic location: head, neck, trunk, extremities, inguinal, perirectal, buttocks, and external genitalia.

RESULTS

Of the 584 wounds, 36 (10 postsurgical wounds) were in the head, 16 (five postsurgical wounds) in the neck, 222 (105 postsurgical wounds) in the trunk, 15 (one postsurgical wound) in the arm, 60 in the hand, 181 (29 postsurgical wounds) in the leg, 18 (eight postsurgical wounds) inguinal, 22 (five postsurgical wounds) in the buttocks, seven perirectal, and 13 (three postsurgical wounds) in the external genitalia.

In wounds, aerobic or facultative bacteria were present in 223 specimens (38%), anaerobes in only 177 specimens (30%), and mixed aerobic-anaerobic flora in 184 specimens (32%). In total there were 1470 isolates, 558 aerobic or facultative and 912 anaerobic bacteria, an average of 2.5 isolates per wound (1.6 anaerobes and 0.9 aerobes or facultative bacteria) (Tables 1 and 2).

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Table 1.—Aerobic and Facultative Organisms Isolated From 584 Wounds

	No. of Isolates										
Organism	**Head**	**Neck**	**Trunk**	**Arm**	**Hand**	**Leg**	**Inguinal**	**Buttocks**	**Perirectal**	**External Genitalia**	**Total**
No. of specimens	30	16	222	15	60	181	18	22	7	13	**584**
Streptococcus											
α-Hemolytic	3	2	34	1	9	9	. . .	2	1	1	**62**
γ-Hemolytic	4	1	4	2	8	6	. . .	1	. . .	1	**27**
Group A	5	3	9	2	16	15	. . .	1	. . .	1	**52**
Group B	. . .	1	. . .	. . .	2	. . .	. . .	. . .	. . .	. . .	**3**
Group D	1	. . .	. . .	. . .	. . .	16	1	3	. . .	. . .	**21**
Staphylococcus aureus	10	7	46	8	26	46	5	3	2	2	**155**
S epidermidis	. . .	1	11	. . .	3	17	2	3	. . .	1	**38**
Proteus species	. . .	. . .	8	. . .	1	8	1	1	1	. . .	**20**
Pseudomonas aeruginosa	. . .	. . .	13	2	3	16	1	2	. . .	. . .	**37**
Other *Pseudomonas* species	2	. . .	2	. . .	1	3	1	. . .	. . .	. . .	**9**
Escherichia coli	. . .	. . .	28	. . .	1	18	2	4	1	2	**56**
Klebsiella pneumoniae	1	. . .	2	. . .	. . .	3	1	3	. . .	. . .	**10**
Enterobacter species	. . .	. . .	2	. . .	. . .	5	. . .	1	. . .	. . .	**8**
Other enterobacteriaceae*	2	1	12	. . .	. . .	21	1	2	1	. . .	**40**
Haemophilus influenzae	2	. . .	. . .	. . .	1	. . .	. . .	. . .	. . .	. . .	**3**
H parainfluenzae	. . .	1	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	**1**
Eikenella corrodens	. . .	. . .	. . .	. . .	6	. . .	. . .	. . .	. . .	. . .	**6**
Neisseria species	1	. . .	. . .	. . .	5	1	. . .	. . .	. . .	. . .	**7**
Candida species	. . .	. . .	. . .	. . .	3	. . .	. . .	. . .	. . .	. . .	**3**
Total	**31**	**17**	**171**	**15**	**85**	**184**	**15**	**26**	**6**	**8**	**558**

*Other enterobacteriaceae include *Klebsiella* species other than *K pneumoniae*, *Citrobacter* species, *Providencia* species, *Morganella* species, *Acinetobacter* species, and *Aeromonas* species.

Deep intra-abdominal or truncal infection was also present in 46 patients. Organisms similar to those isolated from wounds or cutaneous abscesses were also recovered from deep infections in 31 (67%) of these patients.

In abscesses, aerobic or facultative organisms were recovered from 177 specimens (26%), anaerobic bacteria from only 243 specimens (36%), and mixed aerobic-anaerobic flora from 256 specimens (38%). In total there were 1702 isolates, 602 aerobic or facultative and 1100 anaerobic bacteria, an average of 2.5 isolates per abscess (1.6 anaerobes and 0.9 aerobes or facultative bacteria; range, one to seven isolates per specimen) (Tables 3 and 4).

The number of isolates per infected site varied between one and seven. The average number of isolates per infected site is reported in Table 5. The rate of recovery of anaerobic bacteria was almost always higher than the rate of recovery of aerobic or facultative organisms. The highest rate of recovery of anaerobes in wounds was in the inguinal, buttocks, and trunk areas, and in abscesses in the perirectal, external genitalia, neck, and inguinal areas. One hundred thirty-four wounds (23%) and 160 abscesses (24%) yielded only one organism. *Staphlyococcus aureus* was the most common organism, found in 218 cases (74%). Twenty-nine wounds and 41 abscesses yielded a pure culture of a single anaerobe, including 44 isolates of *Bacteroides* species (13 *Bacteroides fragilis*, six *Bacteroides melaninogenicus*, six *Bacteroides intermedius*, five *Bacteroides thetaiotaomicron*, four *Bacteroides distasonis*, four *Bacteroides vulgatus*, and two each of *Bacteroides disiens*, *Bacteroides oralis*, and *Bacteroides asaccharolyticus*) 12 isolates of *Clostridium* species, seven isolates of *Fusobacterium* species, five isolates of *Peptostreptococcus* species, and two isolates of *Propionibacterium acnes*.

In the 184 wounds and 256 abscesses where polymicrobial aerobic-anaerobic infection was observed, several bacterial combinations were noted: the *B fragilis* group was recovered with *Escherischia coli* 36 times, with *S aureus* 18 times, and with group D streptococcus 15 times. The *B melaninogenicus* group was isolated with group A streptococcus in 30 instances and with *S aureus* in 11 instances. Anaerobic cocci were recovered with *E coli* in 34 cases, with group A streptococcus in 15 cases, and with *S aureus* in nine cases.

Tables 1 to 4 record the major types of isolated bacteria. The predominant aerobic organisms were *S aureus* (208 isolates in abscesses and 155 in wounds), group A streptococci (46 isolates in abscesses and 52 in wounds), and *E coli* (41 isolates in abscesses and 56 in wounds). The predominant anaerobic organisms were *Bacteroides* species (586 isolates in abscesses and 400 in wounds), gram-positive cocci (296 isolates in abscesses and 280 in wounds), *Clostridium* species (46 isolates in abscesses and 107 in wounds) and *Fusobacterium* species (84 isolates in abscesses and 25 in wounds).

The distribution of aerobic and facultative organisms showed the following trends: *S aureus* was recovered from abscesses in all body sites but predominated (highest number of isolates per sample) in infections of the leg (0.6 isolates per specimen), neck (0.5 isolates per specimen), and hand (0.5 isolates per specimen). *Staphylococcus aureus* was recovered least often from abscesses and wounds of the perirectal and external genitalia areas. Group D *streptococci*, *E coli*, and *Neisseria gonorrhoeae* were mostly isolated from abscesses in the external genitalia and perirectal areas, and *Haemophilus influenzae* was mostly isolated from abscesses of the head and neck. *Proteus* and *Pseudomonas* species were mostly removed from abscesses in the trunk, head, and perirectal areas. In wounds, the highest recovery rates for all gram-negative organisms were in the trunk and buttocks areas.

The following trends were noted regarding distribution of anaerobic organisms: Anaerobic gram-positive cocci were iso-

Table 2.—Anaerobic Organisms Isolated From 584 Wounds

	No. of Isolates										
Organism	Head	Neck	Trunk	Arm	Hand	Leg	Inguinal	Buttocks	Perirectal	External Genitalia	Total
No. of specimens	30	16	222	15	60	181	18	22	7	13	**584**
Peptostreptococcus magnus	3	2	26	1	9	24	4	1	1	2	**73**
P micros	...	1	7	...	1	...	...	...	...	...	**9**
P asaccharolyticus	...	3	16	1	2	20	1	...	1	...	**44**
P morbilorum	3	...	...	...	...	...	...	3	...	...	**6**
P prevotii	1	1	14	1	6	25	2	2	...	3	**55**
P saccharolyticus	...	...	4	...	...	3	1	1	...	...	**9**
P anaerobius	2	2	13	...	3	...	1	2	...	3	**26**
Other *Peptostreptococcus* species	5	3	17	2	3	18	2	2	1	...	**53**
Streptococcus intermedius	1	...	...	...	1	2	...	...	...	...	**4**
S constellatus	...	...	1	...	...	...	...	...	...	...	**1**
Veillonella parvula	...	...	4	1	1	4	...	...	...	...	**10**
V alcalescens	1	...	...	...	...	2	...	...	...	1	**4**
Other *Veillonella* species	...	...	1	...	...	...	...	...	...	...	**1**
Gaffkya species	...	...	3	...	...	...	...	...	...	...	**3**
Bifidobacterium species	1	...	...	...	...	...	...	...	...	...	**1**
Eubacterium lentum	...	...	8	...	1	2	...	1	...	...	**12**
Other *Eubacterium* species	1	...	3	...	...	...	...	...	...	...	**4**
Proprionibacterium acnes	8	3	19	2	11	8	...	1	...	...	**52**
Other *Proprionibacterium* species	...	...	3	...	...	...	1	1	...	...	**5**
Lactobacillus species	...	...	5	...	...	1	...	...	...	...	**6**
Clostridium septicum	...	...	...	...	...	1	...	1	...	...	**2**
C difficile	...	...	1	...	...	...	...	...	...	...	**1**
C perfringens	1	...	22	2	1	19	1	...	...	2	**48**
Other *Clostridium* species	...	2	25	2	6	17	2	4	...	...	**58**
Fusobacterium nucleatum	...	...	4	2	9	...	...	...	...	...	**15**
F varium	...	...	1	...	...	1	...	...	...	...	**2**
Other *Fusobacterium* species	1	...	2	1	1	2	...	...	1	...	**8**
*Bacteroides fragilis**	1	2	84	...	3	36	6	5	3	1	**141**
*B distasonis**	...	...	4	1	...	6	1	1	...	...	**13**
*B ovatus**	1	...	4	...	...	4	...	...	...	1	**10**
*B vulgatus**	...	...	2	...	...	4	...	...	...	...	**6**
*B thetaiotaomicron**	...	...	19	1	5	5	2	1	...	1	**34**
*B uniformis**	1	...	2	...	...	...	...	...	...	...	**3**
B melaninogenicus	3	1	6	1	5	5	2	2	...	1	**26**
B intermedius	1	1	10	1	4	6	...	1	2	...	**26**
B asaccharolyticus	2	1	7	...	4	13	1	1	...	...	**29**
B ureolyticus	1	1	4	...	2	7	3	1	...	...	**19**
B oralis	...	...	3	...	1	1	...	...	...	...	**5**
B bivius	...	...	12	...	1	7	...	1	1	2	**24**
B disiens	...	...	1	...	...	...	...	1	...	...	**2**
B oris-buccae	...	...	...	...	1	...	...	...	...	...	**1**
Other *Bacteroides* species	1	1	26	3	8	16	...	4	...	2	**61**
Total	**39**	**24**	**383**	**22**	**89**	**259**	**30**	**37**	**10**	**19**	**912**

*These species all belong to the *B fragilis* group.

lated from wounds and abscesses in all sites, and their rate of recovery was between 0.3 to 0.6 isolates per specimen. However, the highest rates of isolates per abscess were in the neck (0.7 isolates per specimen) and perirectal (0.6 isolates per specimen) areas. In wounds, the highest rates of recovery were in the neck (0.6 isolates per specimen), inguinal (0.6 isolates per specimen), and external genitalia (0.6 isolates per specimen) areas. *Clostridium* species were mostly recovered in abscesses of the trunk, perirectal, buttocks, and external genitalia areas and in wounds of the trunk, leg, and hand areas. *Fusobacterium* species were mostly isolated from abscesses of the head, neck, and perirectal areas, and the *B fragilis* group was mostly isolated from abscesses of the perirectal (0.6 isolates per specimen), trunk (0.6 isolates per specimen), and external genitalia (0.5 isolates per specimen) areas. In wounds, the *B fragilis* group was mainly isolated in the trunk (0.5 isolates per specimen), inguinal (0.5 isolates per specimen), and leg (0.3 isolates per specimen) areas.

Table 3.—Aerobic and Facultative Organisms Recovered From 676 Cutaneous Abscesses

	No. of Isolates											
Organism	**Head**	**Neck**	**Breast**	**Trunk**	**Arm**	**Hand**	**Leg**	**Inguinal**	**Buttocks**	**Perirectal**	**External Genitalia**	**Total**
No. of specimens	158	43	40	123	13	21	12	32	35	136	63	**676**
Streptococcus												
α-Hemolytic	11	5	8	18	2	3	1	1	2	5	...	**56**
γ-Hemolytic	3	...	1	11	1	1	...	...	...	2	1	**20**
Group A	12	9	3	2	4	4	1	2	...	8	1	**46**
Group B	4	...	...	...	...	...	...	...	1	2	...	**7**
Group C	...	1	...	...	...	...	...	...	...	...	...	**1**
Group D	...	...	...	7	...	1	...	2	1	7	7	**25**
Staphylococcus aureus	49	22	11	42	5	10	7	9	12	33	8	**208**
S epidermidis	6	2	2	10	1	2	...	...	...	6	4	**33**
Neisseria gonorrhoeae	2	...	...	...	...	...	...	...	...	2	5	**9**
Proteus species	2	...	2	5	...	...	...	3	2	11	5	**30**
Pseudomonas aeruginosa	3	...	...	12	...	...	...	1	1	4	...	**21**
Other *Pseudomonas* species	6	...	...	8	1	1	...	...	1	3	2	**22**
Escherichia coli	2	...	1	...	...	...	1	1	3	17	16	**41**
Klebsiella pneumoniae	4	...	...	1	...	...	1	1	...	3	2	**12**
Enterobacter species	1	1	...	3	...	...	...	...	...	1	1	**7**
Other enterobacteriaceae*	3	...	...	9	...	2	2	2	3	15	3	**39**
Haemophilus influenzae	10	1	...	...	...	...	...	...	...	...	...	**11**
H parainfluenzae	5	...	...	...	...	1	...	...	...	...	...	**6**
Eikenella corrodens	...	...	...	...	...	2	...	...	...	...	...	**2**
Lactobacillus species	...	...	...	...	...	...	...	...	...	3	...	**3**
Candida species	...	...	...	2	...	1	...	...	...	...	...	**3**
Total	**123**	**41**	**28**	**130**	**14**	**28**	**13**	**22**	**26**	**122**	**55**	**602**

*Other enterobacteriaceae include *Klebsiella* species other than *K pneumoniae, Citrobacter* species, *Providencia* species, *Morganella* species, *Acinetobacter* species, and *Aeromonas* species.

The *B melaninogenicus* group was mostly isolated in abscesses of the arm (0.6 isolates per specimen), head (0.4 isolates per specimen), perirectal (0.4 isolates per specimen), and neck (0.3 isolates per specimen) areas. In wounds, the *B melaninogenicus* group predominated in the hand (0.2 isolates per specimen) and head (0.2 isolates per specimen) areas. *Bacteroides bivius* was mostly recovered in abscesses of the perirectal area and in wounds of the external genitalia, leg, and trunk areas.

Bacteremia caused by organisms identical to those found in wounds occurred in 78 instances (13% of all wounds), and bacteremia caused by organisms identical to those recovered in abscesses occurred in 76 cases (11% of all abscesses) (Table 6). The highest numbers of isolates were the *B fragilis* group (60 isolates, including 45 *B fragilis*, seven *B thetaiotamicron*, six *B distastonis*, and two *B vulgatus*), *Clostridum* species (21 isolates), *S aureus* (21 isolates), and enterobacteriaceae (15 isolates).

Analysis showed no significant reduction in the isolation rate of organisms in patients who received antimicrobial therapy prior to sample collection. Evaluation of the microbiological data according to the patients' ages showed no significant correlation between the age and the bacterial isolates, except for the higher recovery rate of *H influenzae* and group B *Streptococcus* in children younger than 2 years and the infrequent recovery of the *B fragilis* group in this age group.

COMMENT

This study demonstrates the importance of anaerobic bacteria in cutaneous abscesses and wounds. Although *S aureus* was the predominant isolate, especially in infections in the extremities and the trunk, anaerobes were frequently isolated, and the number of anaerobic bacteria exceeded the number of aerobic and facultative bacteria in cutaneous abscesses and wounds in the perirectal, external genitalia, buttocks, inguinal, neck, and trunk areas. The recovery rate of anaerobes in these sites as reported in this study is similar to the isolation rates of anaerobes in other studies that have investigated the microbiologic characteristics of subcutaneous abscesses in adults[1] and children.[2] Anaerobes were isolated in these studies in numbers similar to or greater than aerobes in abscesses proximal to the oral, rectal, and vulvovaginal areas. These findings are not surprising, since anaerobes predominate in the normal mucous membrane flora in these sites, reaching concentrations of 1×10^{11} in the rectum and 1×10^{9} in the oral cavity, outnumbering aerobes 1000 to 1 in the rectum and between 10 and 100 to 1 in the oral cavity.[8,9] These normal flora isolates are sometimes associated with local cutaneous abscesses and wounds in these areas.

In contrast to previous reports, the present study demonstrates a higher frequency of isolation of the *B fragilis* group in particular and anaerobes in general in trunk and leg wounds and abscesses. This may be due to the inclusion in our report of only specimens submitted for the recovery of both aerobic and anaerobic bacteria. Furthermore, about half of the trunk wounds and cutaneous abscesses followed abdominal surgical procedures that probably involved seeding with organisms of gastrointestinal origin.

The location of the cutaneous abscesses and wounds is of paramount importance in determining the organisms involved in the infection. Aspirates from infection in and around the oral, rectal, and vulvovaginal regions tend to yield mixed

Table 4.—Anaerobic Organisms Recovered by 676 Cutaneous Abscesses

	No. of Isolates											
Organism	**Head**	**Neck**	**Breast**	**Trunk**	**Arm**	**Hand**	**Leg**	**Inguinal**	**Buttocks**	**Perirectal**	**External Genitalia**	**Total**
No. of specimens	158	43	40	123	13	21	12	32	35	136	63	676
Peptostreptococcus magnus	15	6	5	13	3	...	...	2	4	10	2	**60**
P micros	5	2	...	1	...	1	1	1	...	...	1	**12**
P asaccharolyticus	3	2	4	5	...	1	1	1	1	13	9	**40**
P morbilorum	1	...	1	...	...	...	...	...	...	...	...	**2**
P prevotii	5	4	1	3	...	...	1	...	1	5	3	**23**
P saccharolyticus	1	1	...	3	...	...	...	4	...	1	4	**14**
P anaerobius	6	4	3	5	...	...	1	...	2	13	8	**42**
Other *Peptostreptococcus* species	23	7	6	9	1	4	...	5	5	25	6	**91**
Microaerophilic streptococci	...	...	1	...	...	...	...	3	3	...	...	**7**
Streptococcus intermedius	5	2	...	2	...	...	...	...	...	1	...	**10**
Veillonella parvula	7	1	...	2	...	1	...	...	...	4	2	**17**
V alcalescens	...	...	...	...	...	...	...	...	...	1	...	**1**
Other *Veillonella* species	2	...	...	2	...	...	...	...	...	...	...	**4**
Bifidobacterium species	...	2	...	...	...	...	...	...	...	...	...	**2**
Eubacterium lentum	1	1	1	5	...	...	...	...	...	9	4	**21**
Other *Eubacterium* species	...	1	...	2	...	...	...	...	1	2	1	**7**
Proprionibacterium acnes	5	5	3	3	...	1	1	1	1	...	3	**23**
Other *Proprionibacterium* species	3	...	2	...	...	...	...	2	...	...	...	**7**
Lactobacillus species	...	...	...	...	...	...	...	2	...	1	...	**3**
Clostridium perfringens	1	1	...	6	...	...	...	...	1	2	1	**12**
C butyricum	...	...	...	1	...	...	...	...	...	1	...	**2**
Other *Clostridium* species	...	1	1	13	...	...	...	...	3	8	6	**32**
Fusobacterium varium	...	...	...	1	1	...	...	...	...	...	1	**3**
F nucleatum	16	3	3	2	...	...	1	1	1	6	3	**36**
F mortiferum	2	...	1	...	...	...	...	...	...	1	1	**5**
F necrophorum	1	1	...	...	...	...	...	...	...	...	1	**3**
Other *Fusobacterium* species	12	1	...	6	...	...	1	1	2	13	1	**37**
*Bacteroides fragilis**	3	3	2	54	2	1	2	3	5	54	20	**149**
*B distasonis**	...	1	...	5	...	...	...	...	...	2	1	**9**
*B ovatus**	2	...	...	5	1	...	...	1	1	8	3	**21**
*B vulgatus**	1	1	1	...	...	...	...	1	1	3	2	**10**
*B thetaiotaomicron**	...	...	...	6	...	...	...	4	2	11	4	**27**
*B uniformis**	...	...	...	...	...	...	...	1	1	...	2	**4**
B melaninogenicus	34	6	2	2	4	1	...	2	1	17	4	**73**
B intermedius	21	1	3	...	2	1	...	...	...	11	5	**44**
B asaccharolyticus	19	6	1	1	1	...	1	...	3	20	4	**56**
B ureolyticus	7	...	7	4	3	1	...	10	4	27	8	**71**
B oralis	7	3	2	...	...	1	...	4	...	1	1	**19**
B bivius	...	...	...	2	1	...	1	3	1	9	3	**20**
B disiens	...	...	...	...	...	...	...	1	...	1	...	**2**
B oris-buccae	3	1	...	1	...	...	...	1	...	2	...	**8**
Other *Bacteroides* species	15	5	6	5	3	2	...	4	5	19	7	**71**
Total	**226**	**72**	**56**	**169**	**22**	**15**	**11**	**58**	**49**	**301**	**121**	**1100**

*These species all belong to the *B fragilis* group.

aerobic and anaerobic flora similar to those that are part of the normal microbial flora at the adjacent mucous membrane. Conversely, specimens obtained from areas remote from those sites primarily contained constituents of the microflora indigenous to the skin.

Mixed aerobic and anaerobic infections are also more prevalent in the breast area, fingers, and nail beds.[2] This finding may be due to the direct introduction of mouth flora (which are predominantly anaerobic) by sucking or biting.

The data presented illustrate the relative frequencies of isolation of *Bacteroides*, *Peptostreptococcus*, *Clostridium*, and *Fusobacterium* species in various infections. About 91% of the anaerobic bacteria recovered from the infections examined were members of these genera. The polymicrobial nature of the infections also was highlighted in the data; the average number of isolates per specimen was 2.5. Although the pathogenic role of all bacterial isolates has not been established, the synergistic characteristics in polymicrobial infec-

Table 5.—Bacteriological Characterization

	Wounds										
	Head	Neck	Trunk	Arm	Hand	Leg	Inguinal	Buttocks	Perirectal	External Genital	Total
No. of specimens	30	16	222	15	60	181	18	22	7	13	**584**
Type of bacterial growth, No. of specimens											
Aerobic only	9	3	76	10	19	98	2	5	. . .	1	**223**
Anaerobic only	12	8	55	2	13	59	9	9	4	6	**177**
Aerobic and anaerobic	9	5	91	3	28	24	7	8	3	6	**184**
No. of bacterial isolates per specimen											
Aerobic	1.0	1.1	0.8	1.0	1.4	1.0	0.8	1.2	0.9	0.6	0.9
Anaerobic	1.3	1.5	1.7	1.5	1.5	1.4	1.7	1.7	1.4	1.5	1.6
Total	**2.3**	**2.6**	**2.5**	**2.5**	**2.9**	**2.4**	**2.5**	**2.9**	**2.3**	**2.1**	**2.5**

*Values do not add to total because of rounding error.

Table 6.—Organisms Isolated From Blood of 676 Patients' Abscesses and 584 Patients' Wounds

Organism	No. of Isolates in Blood/ Total No. of Isolates in Abscesses (%)		No. of Isolates in Blood/ Total No. of Isolates in Wounds (%)	
Aerobic				
Staphylococcus aureus	11/208	(5)	10/155	(6)
Group A *Streptococcus*	3/46	(7)	2/52	(4)
Pseudomonas species	7/43	(16)	6/46	(13)
Escherichia coli	2/41	(5)	4/56	(7)
Other enteroacteriaceae	5/58	(9)	4/58	(7)
Subtotal	**28*/396**	(7)	**26†/367**	(7)
Anaerobic				
Peptostreptococcus species	5/296	(2)	8/263	(3)
Clostridium species	2/44	(5)	19/109	(17)
Fusobacterium species	3/84	(4)	1/25	(4)
Bacteroides bivius	1/20	(5)	1/24	(4)
B fragilis group	38/216	(18)	22/204	(11)
B melaninogenicus group	4/183	(2)	1/87	(1)
Other *Bacteroides* species	7/148	(5)	5/194	(3)
Subtotal	**60‡/991**	(6)	**57§/906**	(6)
Total	**88‖/1387**	(6)	**83#/1273**	(6)

*There were 26 patients.
†There were 25 patients.
‡There were 53 patients.
§There were 56 patients.
‖There were 76 patients.
#There were 78 patients.

tions have been well established.[11-13] Several hypotheses have been proposed to explain such microbial synergy. It may be due to mutual protection from phagocytosis and intracellular killing,[14] production of essential growth factors,[15] and/or lowering of oxidation reduction potentials in host tissues.[16] The virulence of *Bacteroides, Clostridium, Peptostreptococcus,* and *Fusobacterium* species is well documented in animal studies[13] and for clinical infections.[17,18]

In past studies *Bacteroides* species were the most frequently recovered anaerobes[1-4]; in this report they accounted for 49% of all anaerobic isolates. The relative distribution of the different *Bacteroides* species has important implications for the management of infections because of the differing antimicrobial susceptibilities of various *Bacteroides* species. Although most members of the *B fragilis* group produce β-lactamase and resist penicillin, their susceptibility to cephalosporins varies[19] but is predictable.[20] The members of the *B fragilis* group are the most prevalent *Bacteroides* species isolated, and *B fragilis* is the most prevalent organism in the group, accouting for 69% of isolates in abscesses and in wounds and 75% of isolates in blood. However, the other members of the *B fragilis* group are more resistant than *B fragilis* to the newer cephalosporins.[19]

The growing resistance of *Bacteroides* species previously susceptible to penicillins has been noticed in the last decade.[17] These are members of the *B melaninogenicus* group, *B oralis, B disiens, B bivius, B oris,* and *B buccae.* The main mechanism of resistance is through the production of the enzyme β-lactamase. When choices are made between antimicrobial agents for the therapy of infections involving *Bacteroides* species, complete identification and testing for antimicrobial susceptibility and β-lactamase production are important.

The recovery rate of *Bacteroides* species in infected sites is similar to their distribution in normal flora.[8,9,17,18] While members of the *B fragilis* group were more often isolated from sites proximal to the gastrointestinal tract, strains of pigmented *Bacteroides* species were more prevalent in infections proximal to the oral cavity, and *B disiens* and *B bivius* were more often isolated from vulvovaginal area. Knowledge of this distribution allows a logical choice of antimicrobial agents adequate for the therapy of infections in these sites.

As in previous studies,[1-4] anaerobic cocci were the second most frequently recovered anaerobes (29% of anaerobic isolates). The predominance of *Peptostreptococcus magnus* was previously established.[21] Anaerobic cocci have been shown to possess virulence in animals infected with them alone,[22] but more so in synergy with other aerobic and anaerobic bacteria.[13] While clostridia (8% of all anaerobes) were mostly found in abscesses and wounds around the rectal or vulvovaginal area, fusobacteria (5% of all anaerobes) were isolated from wounds and abscesses in and around the oral area. This corresponds to the presence as part of the normal host flora in these sites.[8,9]

Staphylococcus aureus, the most prevalent aerobe, was usually found alone. This organism has a well-recognized propensity for abscess formation, both in local and in visceral infections. In contrast to anaerobes, its potential for abscess formation is not as dependent on synergistic bacterial mixtures.[18]

The recovery rate of aerobic and facultative organisms was also correlated with the site of infection. Oral flora, such as *H influenzae,* predominated in head and neck infections, genital

34 Wounds and 676 Cutaneous Abscesses

Abscesses											
Head	**Neck**	**Breast**	**Trunk**	**Arm**	**Hand**	**Leg**	**Inguinal**	**Buttocks**	**Perirectal**	**External Genital**	**Total**
158	43	40	123	13	21	12	32	35	136	63	**676**
45	20	7	53	3	13	8	7	8	9	4	**177**
51	14	18	41	4	4	3	15	15	55	23	**243**
62	9	15	29	6	4	1	10	12	72	36	**256**
0.8	1.0	0.7	1.1	1.1	1.3	1.1	0.7	0.7	0.9	0.9	0.9
1.4	1.7	1.4	1.3	1.7	0.7	0.9	1.8	1.4	2.2	1.9	1.6
2.2	**2.6**	**2.1**	**2.4**	**2.8**	**2.0**	**2.0**	**2.5**	**2.1**	**3.1**	**2.8**	**2.5**

pathogens such as *N gonorrhoeae* were mostly recovered in external genitalia and perirectal infections, while enterobacteriaceae predominated in rectal, external genital, leg, and trunk infections. Skin flora, such as *S aureus* and *Streptococcus*, showed uniform distribution throughout the different body sites, although they predominated in the extremities.

This study illustrates the importance of obtaining specimens adequate for the recovery of aerobic as well as anaerobic bacteria from wounds and cutaneous abscesses. The observed isolation trends in different body sites and the initial reading of Gram stain results could guide the clinician in selecting an empiric antimicrobial therapy. However, the final choice of antimicrobial agents should be based on isolation of specific organisms, aerobes as well as anaerobes.

Antimicrobial agents may also play an important role in surgical prophylaxis, preventing postsurgical wounds and abscesses, which occurred in about 25% of our patients. A first-generation cephalosporin, such as cefazolin, is generally effective as surgical prophylaxis in sites distant from the oral or rectal area. However, in surgical procedures that involve mucus surfaces (oral, gastrointestinal, or vulvovaginal), coverage against both enterobacteriaceae and the *B fragilis* group is of great importance. Single-agent prophylaxis with cefoxitin sodium is generally the treatment of choice for such prophylaxis.

Surgical drainage is the therapy of choice of cutaneous abscesses and wounds. This is important because the environment of an abscess is detrimental for many antimicrobial agents. The abscess capsule, the low pH, and the presence of binding proteins or inactivating enzymes (such as β-lactamase) may impair the activity of many antimicrobial agents (especially aminoglycosides). However, the administration of systemic antimicrobial agents may be indicated in selected cases, especially to prevent or treat bacteremia. Antimicrobial therapy for mixed infections due to aerobic and anaerobic bacteria requires the administration of antimicrobial agents effective against both aerobic and anaerobic bacterial components of the infection.[17,18] Antimicrobial agents that provide coverage for *S aureus* as well as anaerobic bacteria include cefoxitin sodium, clindamycin phosphate, imipenem and cilastatin sodium, and the combinations of β-lactamase inhibitor and penicillin and metronidazole hydrochloride and β-lactamase–resistant penicillin. Cefoxitin sodium and imipenem and cilastatin sodium provide also coverage for enterobacteriaceae. However, aminoglycosides or other agents effective against these organisms should be added to the other agents when treating infections that include these bacteria.

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Reinforcement of Colonic Anastomoses With a Laser and Dye–Enhanced Fibrinogen

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• The incidence of anastomotic leakage in colonic surgery is approximately 10%. We evaluated a technique of laser-fibrinogen reinforcement to strengthen experimental colonic anastomoses. The technique consisted of the topical application of indocyanine green dye–enhanced fibrinogen to the serosal surface of two-layer inverting anastomoses, followed by exposure with an 808-nm diode laser. In the 28 rabbits used for this study, mean bursting pressure at time 0 was 108 ± 13 mm Hg in the group receiving anastomoses with sutures alone and 173 ± 20 mm Hg in the group for which the sutured anastomosis was reinforced with laser-fibrinogen. The difference in bursting pressures between the two groups was statistically significant at time 0. However, at 1, 3, 5, and 7 days, the anastomosis became stronger in both groups and the difference in strength was reduced; the sutured group had more exceptionally weak (<110 mm Hg) bonds than the group treated by laser. Thus, laser-fibrinogen reinforcement significantly enhances the early strength of sutured colonic anastomoses. This technique may reduce the incidence of leakage during the first postoperative week and the associated complications in a clinical setting.

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Leakage from colorectal anastomoses using conventional suture techniques occurs in 10% of patients.[1-6] The origin of this complication is most likely related to suture line ischemia, tension, and technical flaws.[7-9] Attempts at reducing colonic anastomotic leakage have included the use of biologic glues.[10-14] Primary laser welding for small-bowel anastomosis has also been attempted.[15-17] Even though the nonsuture techniques create bonds that should be more watertight than sutured counterparts, the bursting pressures appear to be inferior. The use of laser energy with or without biologic glues has not been systematically studied for use in the colon. We evaluated a technique of anastomotic reinforcement using indocyanine green dye–enhanced fibrinogen in conjunction with the diode laser to strengthen conventional two-layer colonic anastomoses.

MATERIALS AND METHODS

Fibrinogen Preparation

Human fresh frozen plasma was transferred to test tubes and placed in a freezer at −80°C for at least 12 hours. The tubes were then thawed at 4°C and centrifuged at 1000*g* for 15 minutes. The supernatant was decanted, leaving the precipitate, fibrinogen. The high viscosity of this solution permits easy manipulation with forceps. Fibrinogen can be stored at −80°C for up to 1 year.[18]

Dye Preparation

Indocyanine green dye (Becton Dickinson, Baltimore, Md) was mixed with normal saline to saturation. The half-life of the solution is approximately 10 hours. The dye has a maximum absorption of 805-nm wavelength light with an absorption coefficient of $2 \times 10^5/m^{-1}$ cm^{-1}.

Laser System

Welding was performed with a diode laser module (System 7200, Spectra-Physics, Mountain View, Calif) coupled to a hand-held focusing optic. This laser consists of a phased array of gallium-aluminum-arsenide semiconductor diodes. The major wavelength output of the laser diode is 808 ± 1 nm. Additional bands of laser energy occur in the visible red spectrum and allow the operator to visualize the spot size of the laser during creation of the weld.

With the addition of a focusing optic, the beam diameter is 2 mm at a distance of 4 cm. The focusing optic allowed for a greater working distance, providing greater visibility of the anastomotic area. Laser power was measured at the output of the focusing optic with a laser power meter (Model 201, Coherent Science Division, Palo Alto, Calif).

In Vivo Bursting Pressure Measurements and Survival Studies

New Zealand white rabbits were made to fast 24 hours before surgery and received 2 mg/kg of gentamicin sulfate and 40 mg/kg of ampicillin sodium intravenously. The same dosage of antibiotics was administered 8 hours after operation. The rabbits were anesthetized with ketamine (35 mg/kg) and xylazine hydrochloride (5 mg/kg). After the abdomen was prepared with alcohol solution, a midline celiotomy was performed and the appendix delivered into the field. In the rabbit, the appendix is a convenient model for studying end-to-end colonic anastomoses without encountering the morbidity associated with procedures on nonprepared bowel. The anastomosis was performed approximately 2 cm from the distal tip of the appendix, taking care not to compromise the blood supply. In all rabbits, anastomosis was performed by a continuous inner layer of 4-0 polyglycolic acid sutures and eight interrupted inverting seromuscular sutures using 4-0 silk. The appendix was kept moist throughout the procedure. In control rabbits, the procedure was terminated at this point and the abdomen closed with 4-0 polyglycolic acid sutures.

In the experimental group, 2 cm^3 of fibrinogen mixed with indocyanine green dye was spread over the suture line, taking care to cover the anastomosis completely. The 808-nm diode laser was operated at 370 mW in the continuous-wave mode (power density, 4.8 W/cm^2). The fiber was held 10 cm from the anastomosis site, with a spot size of approximately 1 mm. Laser energy was applied in a "paintbrush manner" over the fibrin glue. The characteristic drying of the glue to a light brown, and loss of glistening of the fibrin, indicated the end point.

Bursting pressures were determined after inserting and securing a 16-gauge ridged, duckbill valve vessel cannula (DLP Inc, Grand Rapids, Mich) into the appendix distal to the anastomosis. Intraluminal pressures were recorded on a pressure monitor (Datascope 2000, Datascope Corp, Paramus, NJ). Next, the appendix was clamped proximal to the anastomosis and methylene blue–stained saline infused into the viscus until leakage was noted. The bursting pressure was taken as the lowest pressure at which any leakage of methylene blue was observed.

At postoperative days (PODs) 0, 1, 3, 5, or 7, the rabbits were killed and bursting pressures determined, following which the anastomosis sites were harvested. An additional four rabbits were followed up to 1 month after operation. Welded tissue was preserved in a 10% formaldehyde solution buffered to normal pH for hematoxylin-phloxine-saffron or Masson trichrome staining.

RESULTS

In Vivo Bursting Pressure Measurements

The laser-fibrinogen–reinforced welds required a laser application time of approximately 1 minute for an anastomosis

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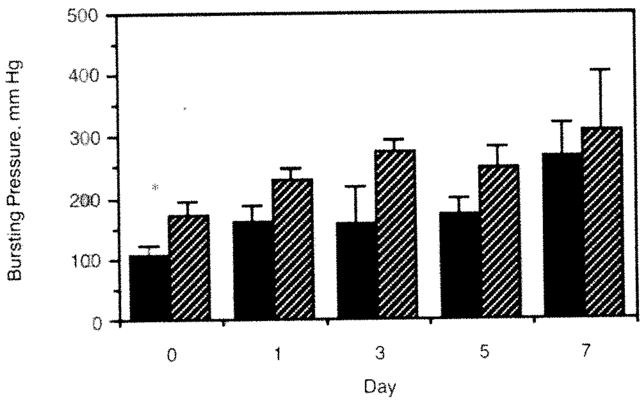

Fig 1.—Appendiceal bursting pressures from time 0 to 7 days following the creation of an anastomosis. The sutured (black bars) and laser-welded (hatched bars) groups' bursting pressures are significantly different immediately after creation (asterisk; $P<.05$).

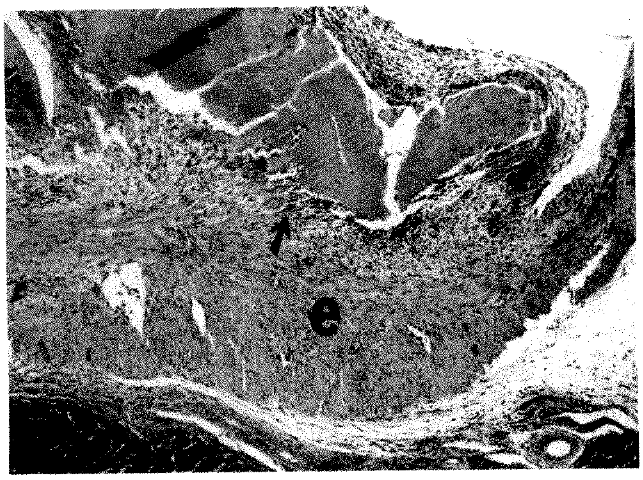

Fig 2.—Postoperative day 5 histologic section of a fibrinogen-welded colon anastomosis reveals an inflammatory reaction to the sutures and fibrinogen and evidence of fibrinogen resorption from the periphery (arrow). The muscularis externa (e) is intact, with no evidence of thermal injury (hematoxylin-phloxine-saffron, ×100).

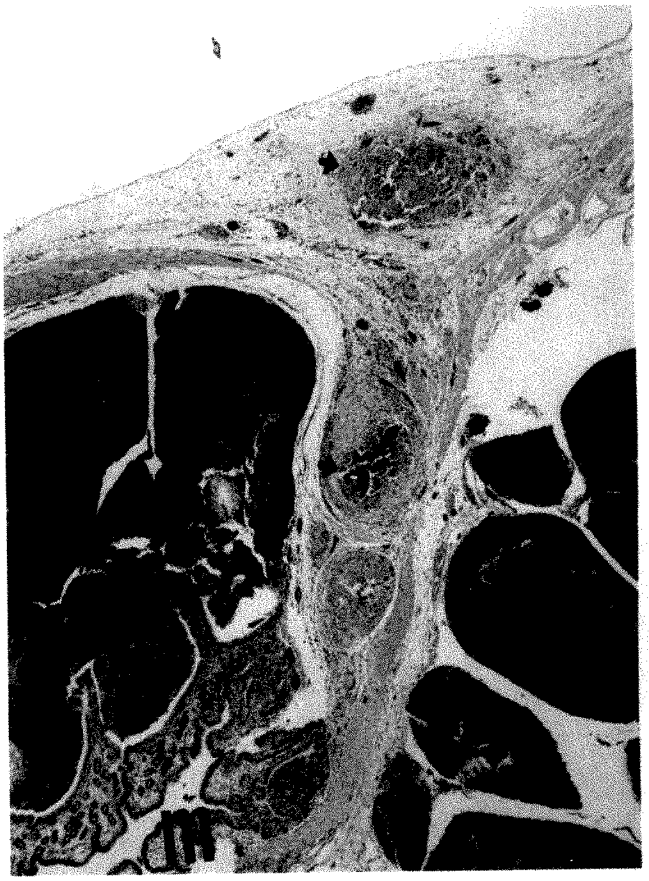

Fig 3.—Postoperative day 24 histologic section of a fibrinogen reinforcement of a sutured colon anastomosis demonstrates complete resorption of the exogenous fibrinogen. No evidence of a foreign body reaction to the fibrinogen is found. The fibrotic reaction to the sutures (arrows) appears to be resolving. The mucosa (m) appears well healed. Lymphoid tissue is prominent in the rabbit appendix (hematoxylin-phloxine-saffron, ×40).

with circumference of 3 cm. At time 0, the bursting pressures of the sutured anastomoses without fibrin glue (108 ± 13 mm Hg, n = 7) were significantly less than those of the anastomoses reinforced with the fibrin glue (173 ± 20 mm Hg, n = 6; $P<.05$) (Fig 1).

Twenty-three rabbits (14 laser-treated, nine sutured) were killed at intervals during the week after operation. The bursting pressures increased in both groups at a similar rate (Fig 1), with pressures in the laser-fibrinogen–reinforced samples being generally higher than in the sutured anastomoses (not significant). In 11 rabbits (eight in the laser-treated group, three in the sutured group), the appendixes burst away from the anastomosis site. The lowest bursting pressure at any time for the laser-treated group was 144 mm Hg (time 0). Seven sutured anastomoses burst at the anastomosis site at pressures less than or equal to 110 mm Hg.

Gross Evaluation

Among the rabbits followed up for 1 to 30 days, no evidence of anastomotic leakage or infection occurred in any of the sutured or laser-fibrinogen–reinforced anastomoses. In the reinforced group, we noted three moderate stenoses (50% of original lumen, PODs 1, 3, and 5) and one complete stenosis of the appendiceal lumen (POD 5). In the sutured group, there was one 50% stenosis noted at POD 3 and two complete stenoses at POD 5.

Histologic Evaluation

Sutured Group.—Within the first week, there was an acute inflammatory response to the sutures followed by infiltration of spindle cells, monocytes, and eosinophils. Occasional foreign body giant cells were noted about the periphery of the sutures. By POD 24, the overall inflammatory response had subsided but there was still focal inflammation, mainly in the periphery of the silk sutures and within the fibers of the polyglycolic sutures. Large clusters of giant multinucleated foreign body cells were also evident.

Fibrin Glue–Soldered Anastomoses.—The histologic appearance of the fibrin glue–anastomotic complex was typified by the following time course. On the first 3 days after operation, the fibrin glue appeared as an eosinophilic amorphous coagulum free of cellular infiltrate. By POD 5, an inflammatory reaction to the sutures and fibrin glue was noted, and there was some resorption of the fibrin glue from the periphery (Fig 2). Proliferation of fibroblasts was noted, although lymphocytes dominated the inflammatory reaction. Very few neutrophils and no giant foreign body cells were noted. By POD 7, there was almost complete resorption and replacement of the fibrinogen by fibroblastic ingrowth. Also by POD

7, colonic mucosa was seen covering the anastomosis in both groups. By POD 24 (Fig 3), there was some resolution of the fibrotic reaction to the sutures, evidenced by less interstitial filling with fibroblasts. No sign of the exogenous fibrinogen could be found.

COMMENT

We have shown that laser-fibrinogen–reinforced rabbit appendiceal anastomoses burst at significantly higher pressures than conventional suture closures. The increase in anastomotic strength persisted throughout the first week following operation.

Approximately one third of the mortality and morbidity associated with colorectal procedures results from anastomotic leakage.[9,19] The most important factors for uncomplicated healing are considered to be adequate blood supply, absence of tension on the anastomosis, and formation of watertight seals.[8,20,21] Prevention of anastomotic leakage during the critical first week following operation should significantly reduce the complications associated with these procedures. Biologic glues and laser welding have been used independently by various investigators in an attempt to achieve this goal; however, joint use of these modalities has not been reported in colonic anastomosis.[10-16]

The first attempts to bond tissue employed cyanoacrylates but were associated with high mortality in experimental animals. Recently, there has been interest in the use of thrombin-activated fibrinogen as a biocompatible tissue sealant. Sutureless colon anastomoses using fibrinogen have been performed[12]; however, the glued anastomoses are weaker than conventional sutures during the critical "lag" period of healing. After 7 days, anastomotic strength, as measured by bursting pressures, demonstrates values similar to those obtained by sutures.[12,17] Similar results have been obtained from studies using this agent for microvascular anastomoses.[22]

A more effective approach for dealing with postoperative leakage has been in the application of fibrin glue to reinforce a sutured anastomosis by forming a watertight seal. In heart transplantation surgery, this technique has allowed a 68% reduction in blood loss.[23] In rectal anastomoses performed on dogs, it has been shown that no leakage occurs when conventional sutured bowel anastomosis is reinforced with fibrin glue applied intraluminally to the mucosa.[1] Fibrin glue has been used to reinforce the anastomoses in 32 patients undergoing colonic resection and anastomosis, with one fatal leakage.[24] Application of the fibrin sealant for low rectal anastomoses has suggested that although leakage is not prevented entirely, the incidence of leakage is reduced.[25] In the absence of a well-controlled randomized trial, the utility of biologic glues in colon anastomoses cannot be determined.

Successful laser tissue welding has been reported in several surgical fields.[26-28] Techniques generally rely on precise primary apposition of the tissue edges and avoidance of thermal injury to exposed tissues. Early disruption due to the diminished strength of welds immediately after creation has prevented more widespread use of this technology. A laser-fibrinogen–reinforced suture anastomosis does not require such precise apposition as an anastomosis primarily made by laser. In addition, the dye-enhanced fibrinogen absorbs most of the laser energy and thus prevents excessive heating of the substrate tissues. Avoidance of excessive heating of the substrate tissues allows greater technical flexibility during the creation of the anastomosis in that imperfections in the suture line after initial use of the laser can be readily repaired by application of additional fibrinogen and laser. Histologically, there appeared to be a greater tendency for fibroblastic response in the laser-fibrinogen–reinforced anastomoses, but the stenosis rate was essentially the same in both groups.

Most comparative studies of colon anastomoses, with or without biologic glues, have looked at postoperative intervals of 7 or more days. We did not observe a significant difference in leakage of pressure at 7 days, suggesting that the colon had achieved significant strength in this time. The most significant difference was observed on PODs 1 and 3, the lag period of anastomotic healing. Our results demonstrate that laser-fibrinogen–reinforced colonic anastomoses are stronger than conventional sutured anastomoses; this improvement may result in a reduction of anastomotic leakage in a clinical setting.

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Hepatic Vein Reconstruction for Preserving Remnant Liver Function

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• Hepatic malignancies often infiltrate to the major hepatic vein. Recently, we performed hepatic resection combined with hepatic vein reconstruction for preserving remnant liver function in three such patients. One patient had a saphenous vein graft. Postoperative liver function of the patients who underwent hepatic vein reconstruction was compared with those of eight patients who underwent hepatic resection of segments VII and VIII. The right hepatic vein in four of them was resected and in the remaining four was preserved by skeletalization using an ultrasonic aspirator. Although four patients with right hepatic vein resection showed severe lowering of liver function after surgery, the postoperative course of patients with preservation or reconstruction of the right hepatic vein maintained good liver function. Liver regeneration of three patients with hepatic vein reconstruction was good on computed tomography. Besides this report, to our knowledge, there is no other report of hepatic vein reconstruction for preserving the remnant liver function. Problems with hepatic resection combined with hepatic vein reconstruc tion are discussed. We conclude that hepatic vein reconstruction is one of the means for extending indication of the malignant tumor resection of the liver.

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Right hepatic lobectomy for hepatocellular carcinoma (HCC) combined with cirrhosis is often limited because of the low level of hepatic function. Accordingly, various procedures for resecting liver cancer located in segments VII and VIII of the liver have been reported.[1] Most of the right lobe of the liver is drained by the right hepatic vein (RHV). Therefore, when a malignant tumor in segments VII and/or VIII compresses or infiltrates the major trunk of the RHV, the RHV is resected together with the tumor for curative resection, and subsequently the main drainage vein of segment VI is ligated. After the procedure, however, it remains unknown as to whether segment VI without a drainage vein can share in the postoperative function of the remnant liver.

We previously reported the results of an animal experiment study, in which we found that the congestive area due to hepatic vein ligation in the remnant liver cannot be expected to function with an available parenchyma in the early postoperative period.[2] Additionally, this problem is more serious in cirrhotic patients with a lower liver function. We have found no reports describing the procedure to overcome this problem. We recently performed hepatic vein reconstruction in three cases for the purpose of preserving a drainage vein of the remnant liver segment. This article reports on the implication of hepatic vein reconstruction in the remnant liver segment.

PATIENTS AND METHODS

Patients

From March 1978 to December 1989, 203 hepatectomies were performed at the Second Department of Surgery of Hamamatsu (Japan) University Hospital. Eleven of these patients (5.4%) are analyzed herein. These patients were divided into three groups (Table 1 and Fig 1). Group A includes four patients who underwent resection of segments VII and VIII combined with RHV resection. Group B consists of four patients with resection of segments VII and VIII, with the RHV being preserved by skeletalization using an ultrasonic aspirator. Of the three patients of group C, the RHV was reconstructed after resection of segments VII and VIII in one patient; the left hepatic vein was reconstructed after systematic subsegmentectomy in one; and the RHV was reconstructed by a patch graft in the remaining one. The patients were nine men and two women averaging 55.8 years in age, ranging from 44 to 65 years.

The histopathological diagnoses of the tumor and chronic liver diseases are listed in Table 1. There was one nonmalignant lesion that was diagnosed as congenital cystic dilatation of the intrahepatic bile ducts in segments II, VII, and VIII, namely, type IV of Arthur's classification,[3] with chronic hepatitis, hepatolithiasis, and suppurative cholangitis. Hepatomas were the most common operative targets. Liver cirrhosis was complicated in five of eight patients with hepatoma, and chronic viral hepatitis in four. There were several reasons for operatively treating the hepatic vein. These reasons were as follows: the tumor was very close to the main hepatic vein in three patients, direct invasion into the main hepatic vein in four, multiple daughter nodules of HCC in three, and a tumor of more than 5 cm in diameter between segments VII and VIII in four. In one patient, an inferior RHV (IRHV) of 8 mm in diameter, which was to be preserved, was injured during dissection of the hepatic parenchyma and ligated.

Surgical Technique

After complete mobilization of the right lobe, the relationship between location of the tumor and vessels in the liver was certified according to Couinaud's nomenclature,[4] and the size and number of the tumors were explored by intraoperative ultrasonography. The presence of an IRHV was confirmed in nine patients (Table 1). Dissection of the hepatic parenchyma was performed using an ultrasonic aspirator under Pringle's maneuver. The RHV of four group A patients was resected, and that of four group B patients was preserved using an ultrasonic aspirator.

Right and left hepatic veins was reconstructed by interpositioning of the graft that was taken from the saphenous vein or the external iliac vein in two patients of group C, respectively. In the latter patient, the resected external iliac vein was reconstructed using a ringed expanded polytetrafluoroethylene graft. The remaining one patient of group C had a patch graft at the RHV.

From the second postoperative day, intravenous administration of 15 000 IU/d of heparin sodium was begun in both patients with vein reconstruction. From the 4th postoperative day, 4 mg/d of warfarin potassium was administered and has been continued to the present.

Assessment of Liver Function Before and After Surgery

Patients were tested for indocyanine green (ICG) tolerance (intravenous administration of 0.5 mg/kg body weight of ICG), prothrombin time, levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and fibrinogen. All were done preoperatively and at 1, 3, 5, 7, 10, and 14 days after surgery, except for the ICG test, which was performed only before surgery. The preoperative blood laboratory data between the three groups are compared in Table 2. The preoperative serum fibrinogen level showed a significant difference only between groups A and B, although both levels were within the normal range. Postoperative hepatic venography was performed on three patients who underwent hepatic vein reconstruction 1 month after surgery.

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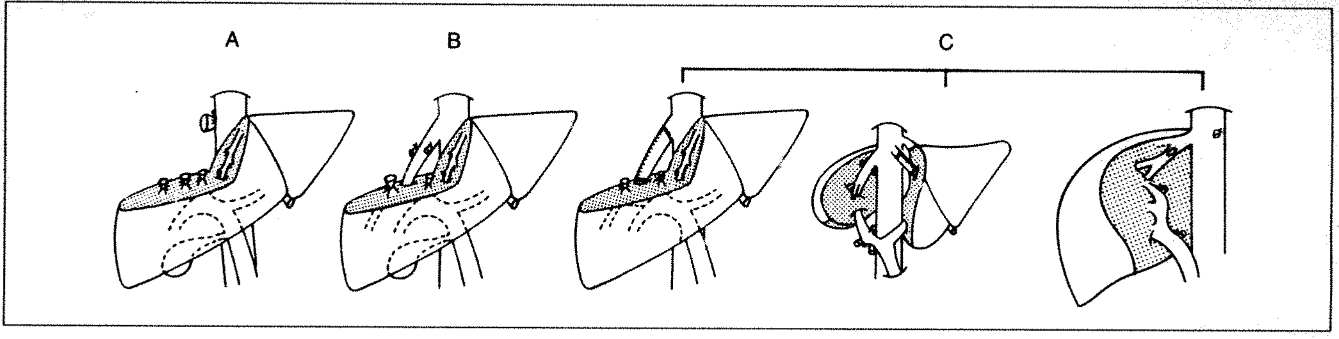

Fig 1.—Classification of liver resection of segments VII and VIII according to hepatic vein treatment.

Table 1.—Grouping of Patients*

Group	Disease	Complicated Liver Disease	RHV	Presence of IRHV No.	Presence of IRHV Diameter, mm
A	HCC	Type B LC	Resected	1	8
	HCC	CH	Resected	2	3 to 5
	HCC	Type B LC	Resected	2	8
	HCC	Type B LC	Resected	2	5
B	HCC	Type B LC	Preserved	3	2 to 3
	HCC	Active CH	Preserved	2	5
	MLC	None	Preserved	3	2 to 3
	CDIBD	CH	Preserved	. . .	. . .
C	MLC	None	Reconstructed†	3‡	8
	HCC	CH	Reconstructed	. . .	
	HCC	Type B LC	Reconstructed	1	10

*HCC indicates hepatocellular carcinoma; LC, liver cirrhosis; MLC, metastatic liver cancer from colon (both were adenocarcinoma); CDIBD, cystic dilatation of intrahepatic bile ducts; RHV, right hepatic vein; IRHV, inferior right hepatic vein; and CH, chronic hepatitis.

†Systematic subsegmentectomy and left hepatic vein reconstruction were performed, but right hepatic vein draining segment VII was preserved.

‡Three short hepatic veins were ligated and cut for resection of segment VI.

Table 2.—Comparison of Preoperative Liver Function Among the Three Groups*

Liver Function	Group A (n=4)	Group B (n=4)	Group C (n=3)
ICG			
R-15′	15.9±5.0	16.4±16	7.7%
KICG	0.129±0.023	0.147±0.05	0.182
PT, %	101±14	111±26	96
AST, U/L	24.5±7.23	17.5±10.1	40
ALT, U/L	16.29±6.74	17.83±10.12	37
TB, μmol/L	13.3±1.5	12.8±6.8	10.7
Fibrinogen, g/L	3.16±1.60†	2.54±1.18†	2.63

*Values are presented as mean±SD. ICG indicates indocyanine green; R-15′, retention rate 15 minutes after injection of ICG; KICG, removal rate of ICG; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; and TB, total bilirubin.

†Fibrinogen level only in serum showed a significant difference ($P<.05$).

Statistical Analysis

The significance of any difference was evaluated by Student's t test, with $P<.05$ being considered significant.

RESULTS

Intraoperative Data

The mean operating time (±SD) of the 10 patients was 266±157 minutes, ranging from 130 to 580 minutes. The amount of bleeding during the operation averaged 1272±705 mL and ranged from 400 to 2319 mL. In three patients with RHV strongly compressed by the tumor, oozing, most probably venous oozing, from the liver stump was a serious problem during dissection of the hepatic parenchyma. There were no significant differences between groups A and B in the operating time, amount of intraoperative bleeding, weight of the resected specimen, and the tumor size. However, three group C patients required a very long operating time in comparison with group A and B patients because of the harvesting of the autovein graft and venous reconstruction.

Mortality and Morbidity

There was one operative death of a group A patient who had retrograde infection along a drainage tube and *Staphylococcus epidermidis* sepsis, as well as massive bleeding from the liver stump that suddenly occurred on the 13th postoperative day. The patient died of hepatic failure on the 16th postoperative day.

Two group A patients and two group B patients had right pleural effusion that was removed by paracentesis and disappeared in all patients within 2 weeks after surgery. Biliary fistula occurred in one group B patient with nonmalignant disease. None of the group C patients had postoperative complication.

Postoperative Liver Function

On the first postoperative day, the AST levels of all group A patients elevated to 292.5 U/L in average ranging from 149.4 to 704.6 U/L. However, those of all group B patients averaged 62.1 U/L, ranging from 50.1 to 87.7 U/L. The AST levels of three group C patients showed a tendency to elevate to the same level as in group A. The AST levels of all patients fell to less than 48.2 U/L within 1 week after surgery. Since the range of fluctuation of AST was large, significant differences were not assessed between the three groups. The postoperative changes in the ALT level presented the same pattern as those of AST. The serum total bilirubin level in only one group A patient remained persistently high (up to 188.1 μmol/L) for a long period after surgery. However, the maximum serum total bilirubin level in patients of groups B and C was 42.75 μmol/L, and fell within the normal level 5 days after operation. The prothrombin time in all group A patients fell to

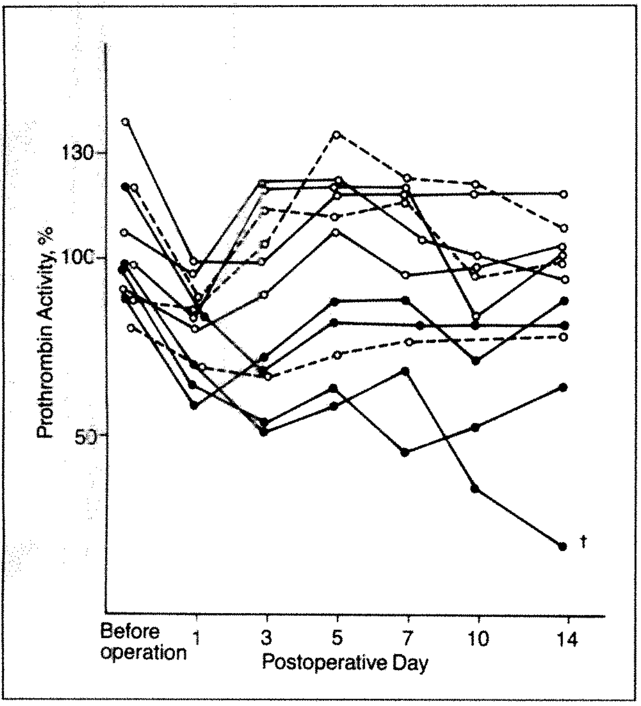

Fig 2.—Postoperative changes of prothrombin time. Solid line with solid circles indicates group A; solid line with open circles, group B; broken line, group C; and dagger, one operative death.

less than 70% after surgery (Fig 2), while those of all group B patients and two of three group C patients remained over 80% through the postoperative course. Although the number of patients was small, there was a significant difference in prothrombin time on the third postoperative day between groups A and B (*P*<.01).

Postoperative Hepatic Venography and Computed Tomography (CT) of the Liver

Hepatic venography was performed 1 month after surgery in all patients who underwent hepatic vein reconstruction. The RHV grafted using the right external iliac vein and the RHV that had a patch graft were completely patent on angiography. Although the saphenous vein graft occluded, the hepatic volume was 1133 cm^3 by CT volumetric determination 1 month after surgery.

Long-term Survival

Long-term survival after operation is summarized in Table 3. Two patients of group A died of recurrence of HCC 6 and 15 months after surgery. All group B and C patients are alive without recurrence of carcinoma, although the follow-up periods of group C patients are short. One group B patient with benign biliary tract disease is doing well without an episode of cholangitis.

One typical patient each of group A and C is presented to emphasize the significance of RHV reconstruction in patients with resection of segments VII and VIII.

Report of Cases

Case 1.—A 53-year-old man was operated on for primary liver cancer on September 4, 1985. He had histopathologically chronic hepatitis and good hepatic function. A tumor 10 cm in maximum diameter located in segments VII and VIII had no tumor capsule and no intrahepatic metastases. Since the tumor was close to the RHV, segments VII and VIII were resected with the RHV. On intraoperative exploration, segment VI had no venous drainage of IRHV.

Table 3.—Results After Liver Resection of Segments VII and VIII With Follow-up Study to June 30, 1989

Group	Diagnosis	No. of Patients	Operative Death	Later Death (Time, mo)	Alive Tumor-Free (Time, mo)
A	Hepatoma	4	1	2 (6, 15)	1 (46)
B	Benign	1	0	0	1 (19)*
	Hepatoma	2	0	0	2 (25, 50)
	Metastatic carcinoma	1	0	0	1 (58)
C	Hepatoma	2	0	0	2 (14, 4)
	Metastatic carcinoma	1	0	0	1 (14)

*This patient has no episode of cholangitis.

Immediately after RHV ligation, the surface of the fifth and sixth segments turned slightly purple. Although the AST level of this patient postoperatively increased to 1464 KU, and the prothrombin time was prolonged to 65%, his postoperative course was uneventful. On the liver scintigrams, the radioisotope uptake of segment VI was sparse 2 weeks after surgery (Fig 3), but slightly increased at 1 month. The liver scintigram 3 years after surgery showed a sufficient radioisotope uptake in segment VI.

Case 2.—A 65-year-old man was admitted in September 1988 for the close examination and surgical treatment of liver tumor. Ultrasonography of the liver disclosed a well-capsulated liver mass 4 cm in diameter between the RHV and the inferior vena cava, and exhibited a dense connection with the RHV (Fig 4). On preoperative hepatic venography and cavography, both large veins were strongly compressed by the tumor, while a short hepatic vein draining segment VI could not be found.

In October 1988, resection of segments VII and VIII with the RHV was performed through a right seventh intercostal thoracoabdominal incision. The inferior vena cava could be easily divided without macroscopic invasion from the tumor. An external iliac vein graft 5 cm in length and 1 cm in width was excised through a newly made extraperitoneal route. After the tumor was removed with the RHV, hepatic vein reconstruction was then carried out using the graft (Fig 5). The blood flow at the surface of segment IV measured by laser doppler blood flowmeter (Advans Co Ltd, Tokyo, Japan) was 19.2, 3.8, and 17.8 mL/min per 100 g of liver tissue before, during, and after RHV reconstruction, respectively. The clamping time of the RHV was 92 minutes. The postoperative course was uneventful. On postoperative hepatic venography, the grafted portion was patent without stenosis (Fig 6, top). A sufficient radioisotope uptake of segment VI was observed on liver scintigram 2 weeks after surgery (Fig 6, bottom). The patient is currently doing well without signs of recurrence of HCC.

COMMENT

Surgical resection is thought to be the only curative treatment for HCC. However, the major hepatic vessels invaded by a tumor must inevitably be resected to obtain a curative resection. When a tumor is located close to the confluence of the hepatic vein and the inferior vena cava, resection of the major hepatic vein with hepatectomy is required. After ligation of the hepatic vein on the peripheral side, however, whether the congestive area is available as a functional volume in the remnant liver has remained controversial.[5-7] Resection of segments VII and VIII combined with RHV resection for patients with a large IRHV has rarely been performed.[1] In this operation, the presence of a large IRHV is very important. Nakamura and Tsuzuki[8] previously reported that 79% of human liver has IRHVs of various sizes. However, whether a small IRHV can sufficiently drain segment VI immediately after ligation of the main RHV is still not known.

When a hepatic vein in the remnant liver was ligated in our previous experiments using rats,[2] the congestive area histologically resulted in necrosis of the hepatic parenchyma 24 hours after ligation. However, good regeneration was seen 4

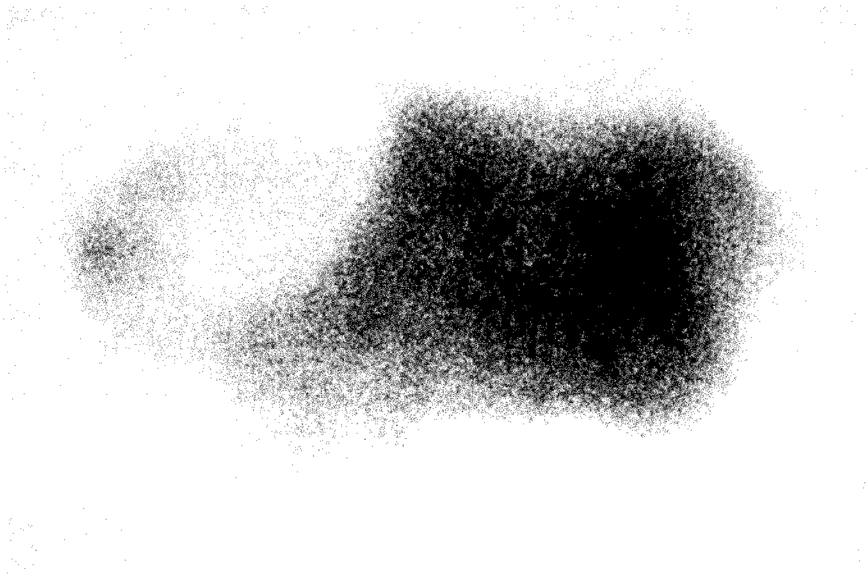

Fig 3.—Liver scintigram 2 weeks after surgery. Radioisotope uptake of the sixth segment decreased in the early postoperative period.

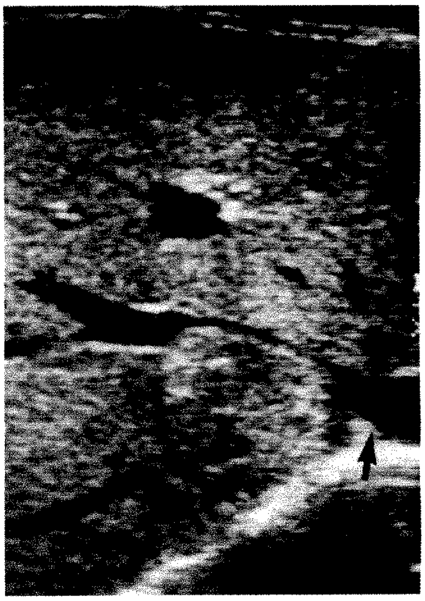

Fig 4.—Preoperative ultrasonography of the tumor in the liver. The tumor is located with a dense connection just below the confluence of the right hepatic vein and inferior vena cava (arrows).

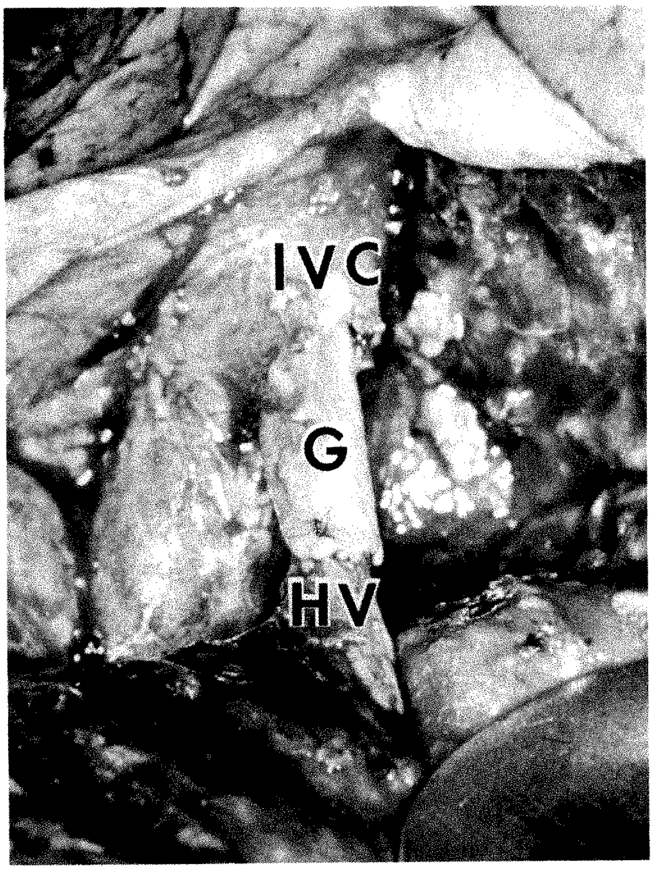

Fig 5.—Right hepatic vein grafted by the right external iliac vein. IVC indicates inferior vena cava; G, grafted vein; and HV, right hepatic vein.

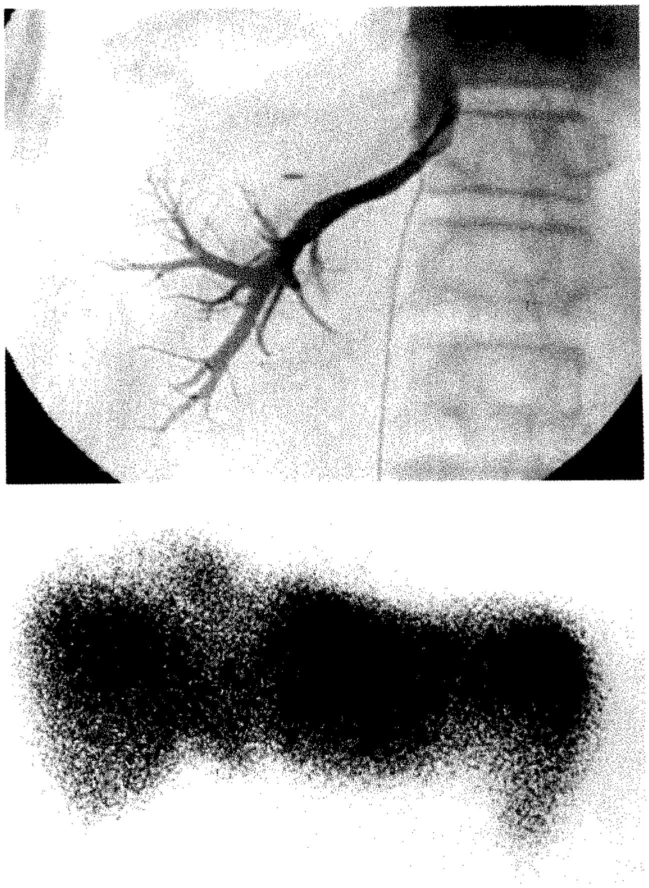

Fig 6.—Top, Postoperative hepatic venography of the patient with a right hepatic vein graft. Bottom, Hepatic scintigram 2 weeks after surgery.

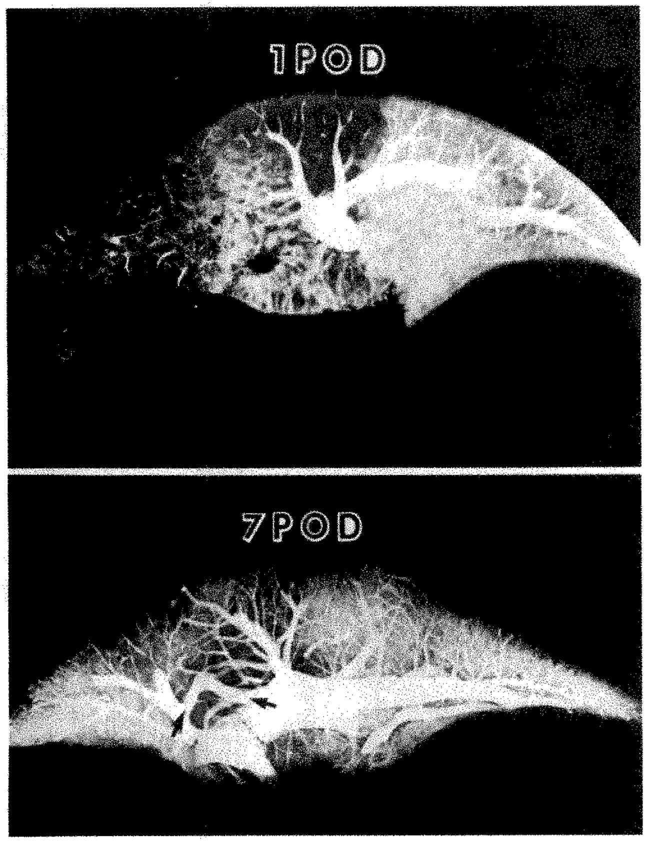

Fig 7.—Hepatic venography of rats on the first postoperative day (top) and seventh postoperative day (bottom) after hepatic vein ligation. Very small communicating veins in the liver could not sufficiently drain the congestive area on the first day after ligation. Arrows show a newly developed intrahepatic collateral vein.

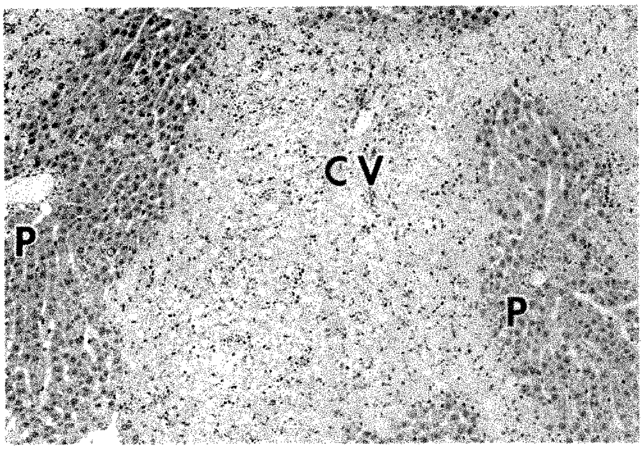

Fig 8.—Central and middle area of the rat liver showed massive necrosis 8 hours after hepatic vein ligation in rats. CV indicates central vein, and P, portal area (hematoxylin-eosin, original magnification ×100).

days after surgery. Moreover, on the seventh day after surgery, intrahepatic venous collaterals for draining the congestive area were observed (Fig 7). However, the area of the liver that had congestion and necrosis (Fig 8) because of hepatic vein ligation was macroscopically atrophic. We thus concluded that the congestive area of the hepatic parenchyma due to hepatic vein ligation cannot be expected as a functional part of the remnant liver. Depinto et al[9] reported that in a patient who underwent middle and left hepatic vein ligations because of blunt abdominal trauma, the left lobe was not visualized on liver scintigram 10 days after surgery. This case supports the result of our experimental study. Furthermore, liver regeneration after hepatectomy was delayed in the patient with cirrhotic liver.[10] Therefore, if there is no large IRHV, RHV reconstruction should be performed for preserving the liver function of segment VI in resection of segments VII and VIII. In the present clinical study, there were significant differences in postoperative liver function between the three groups. This signifies the importance of venous drainage of the remnant liver, which has been supported by our experimental study.

The proper material for hepatic vein grafts should be chosen according to the diameter of the vessels to be reconstructed. A saphenous vein was considered to be a suitable graft for the left hepatic vein of relatively small diameter, but unfortunately it occluded on the venogram 1 month after surgery, possibly due to a small caliber and deformity caused by early regeneration of the remnant liver lobe. This patient, however, had an uneventful postoperative course. The graft may have been patent until development of intrahepatic collaterals as suggested in our experimental study. The external iliac vein may well be indicated for the RHV reconstruction except for one disadvantage, that is, its preparation needs more time. On the other hand, although the patch graft of the hepatic vein can be safely performed, insufficient resection of carcinoma may occur. Concerning these problems, greater experience should be amassed.

There are very few reports of hepatic vein reconstruction. Anastomosis between the inferior vena cava and the left hepatic vein was performed in a patient undergoing split transplantation of the liver.[11] Starzl et al[12] removed of the right hepatic trisegment, retrohepatic vena cava, and left hepatic vein in a patient with hepatic metastases, and performed reconstruction using a reversed cadaver vena cava–iliac vein homograft. No reports have appeared concerning hepatic vein reconstruction considering the remnant liver function after resection of a liver tumor.

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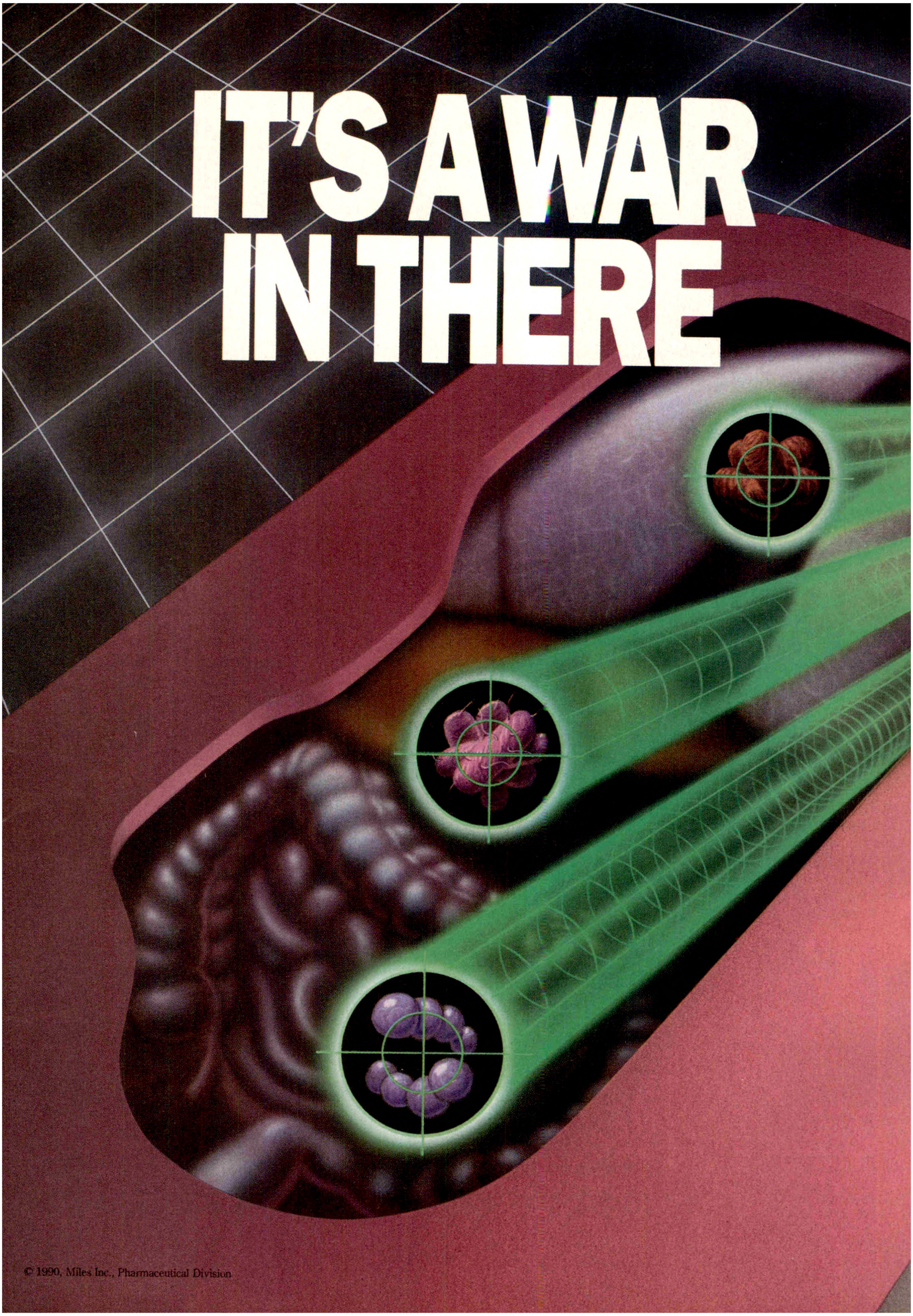

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WARNINGS
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have occurred in patients receiving a penicillin. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with mezlocillin is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to penicillins, cephalosporins or other drugs. Antibiotics should be used with caution in any patient who has demonstrated some form of allergy, particularly to drugs.

If an allergic reaction occurs during therapy with mezlocillin, the drug should be discontinued. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT. EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD BE PROVIDED AS INDICATED.

PRECAUTIONS
Although MEZLIN shares with other penicillins the low potential for toxicity, as with any potent drug, periodic assessment of organ system functions, including renal, hepatic and hematopoietic, is advisable during prolonged therapy. MEZLIN has been reported rarely to cause acute interstitial nephritis.

Bleeding manifestations have occurred in some patients receiving betalactam antibiotics. These reactions have been associated with abnormalities of coagulation tests, such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal impairment. Although MEZLIN has rarely been associated with clinical bleeding, the possibility of this occurring should be kept in mind, particularly in patients with severe renal impairment receiving maximum doses of the drug.

MEZLIN has only rarely been reported to cause hypokalemia; however, the possibility of this occurring should also be kept in mind, particularly when treating patients with fluid and electrolyte imbalance. Periodic monitoring of serum potassium may be advisable in patients receiving prolonged therapy.

MEZLIN is a monosodium salt containing only 42.6 mg (1.85 mEq) of sodium per gram of mezlocillin. This should be considered when treating patients requiring restricted salt intake.

As with any penicillin, an allergic reaction, including anaphylaxis, may occur during MEZLIN administration, particularly in a hypersensitive individual.

As with other antibiotics, prolonged use of MEZLIN may result in overgrowth of non-susceptible organisms. If this occurs, appropriate measures should be taken.

Antimicrobials used in high doses for short periods to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhea should also be evaluated for syphilis. Specimens for dark field examination should be obtained from any suspected primary lesion and serologic tests should be performed. Patients treated with MEZLIN® should undergo follow-up serologic tests three months after therapy.

Interactions with Drugs and Laboratory Tests
As with other penicillins, the mixing of mezlocillin with an aminoglycoside in solutions for parenteral administration can result in substantial inactivation of the aminoglycoside.

Probenecid interferes with the renal tubular secretion of mezlocillin, thereby increasing serum concentrations and prolonging serum half-life of the antibiotic.

High urine concentrations of mezlocillin may produce false positive protein reactions (pseudoproteinurial) with the following methods: sulfosalicylic acid and boiling test, acetic acid test, biuret reaction, and nitric acid test. The bromphenol blue (Multi-stix®) reagent strip test has been reported to be reliable.

Pregnancy Category B
Reproduction studies have been performed in rats and mice at doses up to 2 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus, due to MEZLIN. There are however no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Mezlocillin crosses the placenta and is found in low concentrations in cord blood and amniotic fluid.

Nursing Mothers
Mezlocillin is detected in low concentrations in the milk of nursing mothers, therefore caution should be exercised when MEZLIN is administered to a nursing woman.

ADVERSE REACTIONS
As with other penicillins, the following adverse reactions may occur:

Hypersensitivity reactions: skin rash, pruritus, urticaria, drug fever, acute interstitial nephritis and anaphylactic reactions.

Gastrointestinal disturbances: abnormal taste sensation, nausea, vomiting and diarrhea. If diarrhea persists, pseudomembranous colitis should be considered.

Hematologic and Lymphatic Systems: thrombocytopenia, leukopenia, neutropenia, eosinophilia, reduction of hemoglobin or hematocrit, positive Coombs' test, and hypokalemia.

Abnormalities of hepatic and renal function tests: elevation of serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), serum alkaline phosphatase, serum bilirubin. Elevation of serum creatinine and/or BUN.

Central nervous system: convulsive seizures or neuromuscular hyperirritability.

Local reactions: thrombophlebitis with intravenous administration, pain with intramuscular injection.

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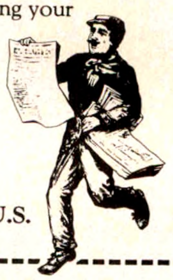

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Evaluation of Methods for Detecting Venous Reflux

Perspectives in Venous Insufficiency

Seshadri Raju, MD, Ruth Fredericks, MD

• Using 793 limbs with nonobstructive venous reflux, we evaluated a number of techniques used for the assessment of venous reflux. The venous Doppler examination was found to be a reliable screening tool with excellent sensitivity and good specificity. Photoplethysmography was 97% sensitive in patients with ambulatory venous hypertension; however, in milder forms of reflux, it was less sensitive. The major drawback of photoplethysmography was the large number of false-positive results obtained. Ambulatory venous pressure measurement and another pressure-based technique, Valsalva-induced foot venous pressure measurement, defined overlapping but different normal and abnormal limbs. Descending venography, when performed as described by Kistner et al, was found to be a reliable tool to assess reflux with more than a 90% sensitivity. The horizontal technique of performing descending venography and nucleotide descending venographies had unacceptably low sensitivity and were abandoned. Features of venous reflux as outlined by these modern technical tools are described.

(*Arch Surg.* 1990;125:1463-1467)

Ambulatory venous pressure measurement has been the traditional "gold standard" for evaluating venous reflux. More recently, numerous other techniques, such as descending venography and photoplethysmography (PPG), have become popular alternative methods of analyzing venous insufficiency. In addition, it is possible to separate venous reflux more accurately from obstruction such that a more selective and "purer" material is available for analysis of venous reflux.[1] Not surprisingly, the newer technology has yielded newer perspectives. In some areas, such as the relationship between superficial and deep venous insufficiency or the etiologic role of perforator incompetence, it has yielded information contrary to long prevalent beliefs. This article presents an evaluation of several available techniques for detecting venous reflux, with emphasis on descending venography.

MATERIALS AND METHODS

Materials

From 1978 to 1987 a total of 1421 limbs were screened for suspected chronic venous insufficiency in the Vascular Laboratory of the University of Mississippi Medical Center, Jackson. Of these, 793 limbs were determined to have nonobstructive chronic venous insufficiency based on laboratory examination and hemodynamic techniques previously described to rule out obstruction.[2] Several limbs were hemodynamically classified as "normal," as no abnormalities were detected by the various laboratory techniques. In addition, data from 30 healthy volunteers were also included as part of the control group of normal limbs. This experience forms the basis of this article. Statistical analysis was carried out using the Kruskal-Wallis method of analysis of variance by ranks.[3]

Methods

Clinical Classification.—Severity of venous reflux was graded clinically as recommended by the Committee on Venous Standards.[4]

Doppler Examination.—A detailed Doppler examination of both limbs, with examination of the femoral, popliteal, saphenous and posttibial veins, was carried out with the patient in the supine position.

PPG.—The technique of PPG for venous congestion was carried out as described by Barnes et al.[5] A tourniquet (30 mm Hg) was used below the knee to differentiate superficial from deep incompetence.

Venous Pressure Measurement.—*The Arm-Foot Venous Pressure Differential and Reactive Hyperemia Tests.*—The arm-foot venous pressure differential and reactive hyperemia tests exclude venous obstruction and have been detailed elsewhere.[1,2]

Ambulatory Venous Pressure Measurement.—Pressures in a dorsal vein of the foot were recorded with the patient standing still, followed by manual compression of the calf several times (usually six to 10 compressions) until the pressure reached a plateau and then recovered to levels recorded before simulated exercise. The efficacy of the manual calf compression technique was validated by comparing it with the traditional "toe-stand" technique (see "Results" section).

In the toe-stand technique, instead of manual compressions, the patient was asked to raise the heel repeatedly to exercise the calf muscles actively until the foot venous pressure reached a plateau.

Valsalva-Induced Foot Venous Pressure Elevation.—The pressure in the dorsal vein of the foot was recorded in the supine patient at

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Table 1.—Evaluation of Techniques Used to Detect Venous Reflux

	Technique Used as Reference ('Gold') Standard for Evaluation*															
	Descending Venography by Kistner et al[7]			Doppler			AVP RT, <16 s			Valsalva-Induced FVP, >4 mm Hg			Presence of Stasis Ulcer		Strip Test During Surgery	
Technique Being Evaluated*	n	% Sensitivity	% Specificity	n	% Sensitivity	% Specificity	n	% Sensitivity	% Specificity	n	% Sensitivity	% Specificity	n	% Sensitivity	n	% Sensitivity
Doppler	208	92	73	...	...	...	360	93	54	360	93	42	87	100	107	89
PPG	208	74	37	814	85	62	389	97	57	315	96	48	87	90	...	...
AVP RT																
<16 s	174	83	77	389	76	81	...	...	...	333	67	73	112	77	...	...
<50% Drop	96	86	78	...	...	...	...	...	...	...	...	...	113	78	...	...
Valsalva-induced FVP, >4 mm Hg	104	74	85	300	86	70	333	66	76	...	...	...	60	87	...	...
Descending venography																
Kistner et al[7]	...	...	...	130	98	89	277	92	60	96	95	45	60	100	107	89
Thomas et al[9]	...	...	...	44	54	89	...	...	...	...	...	...	...	...	...	...
Nucleotide	104	41	71	140	43	74	...	...	...	...	...	...	45	47	...	...

*PPG indicates photoplethysmography; AVP RT, ambulatory venous pressure recovery time; and FVP, foot venous pressure.

rest and with the patient exercising a graduated Valsalva's maneuver to 40 cm of water pressure.[6] The *rise* in foot venous pressure (expressed in millimeters of mercury) with Valsalva's maneuver was the relevant factor for the test.

Ascending Venography.—Ascending venography was performed with the patient in 60° partially erect position with a tourniquet above the patient's ankle.

Descending Venography.—*Descending Venography by Kistner et al.*—Descending venography was performed according to the technique described by Kistner et al.[7] The patient was placed at 60° partially erect position and asked to perform Valsalva's maneuver by blowing against a mercury manometer at 30 to 40 mm Hg. Reflux observed during the Valsalva maneuver was graded according to Kistner's classification as follows: 0, no reflux; 1, reflux of the upper thigh; 2, reflux up to the popliteal; 3, reflux up to the calf veins; or 4, reflux up to the ankle. A different classification[8] based on the number and level of venous systems involved was also evaluated. In the latter method, reflux was classified as involving single level/single system, single level/multiple systems, or multiple level/multiple systems.

Descending Venography by Thomas et al.—In 44 limbs, a supine technique of descending venography recently described by Thomas et al[9] was also evaluated. Reflux was monitored and filmed while the patient executed a Valsalva maneuver in the horizontal position.

Nucleotide Descending Venography.—Technetium Tc 99m albumin colloid was injected via a femoral vein catheter. The technique for eliciting reflux and gradation was similar to that employed for descending venography.

Strip Test for Reflux During Surgery.—The presence of valve reflux can be detected during surgery by performing a strip test.[6] A bulldog clamp is placed on the vein 3 to 4 cms below the valve. Tributaries draining into this segment are either ligated or controlled by silk loops. The venous segment between the valve and the clamp is digitally stripped empty and refilling is observed. A competent valve will prevent retrograde refilling of the emptied venous segment. Reverse Trendelenberg's position of the patient during the maneuver is helpful.

RESULTS

Evaluation of Techniques

The sensitivity and specificity varied according to the "gold standard" utilized for comparison. When stasis ulceration was utilized as a "gold standard" (Table 1), all of the techniques not surprisingly exhibited good to excellent sensitivity. Because stasis ulceration was always associated with reflux, specificity data are lacking under this column. Of course, venous reflux can be present in a milder form without stasis ulceration. A number of techniques, including Doppler, descending venography, ambulatory venous pressure, and Valsalva-induced foot venous pressure elevation, are usable techniques in this context. Unfortunately, there is no agreement as to which of these can be considered a "gold standard." Almost all suffer from shortcomings (see "Comment" section). Table 1, therefore, provides a measure of accuracy for a given technique when a variety of other techniques are used as a "gold standard " For such a comparison, both the technique being evaluated and the referenced "gold standard" should have been performed on the refluxive limb. For a variety of technical and nontechnical reasons, not all techniques were performed on every limb evaluated in the laboratory. The number of limbs tested, therefore, has varied for the various comparisons detailed in Table 1. The number of limbs tested are shown under *n* for calculating sensitivity and specificity data for a given technique.

Doppler Examination.—The Doppler examination was sensitive irrespective of the reference standard used for comparison. The Doppler examination can detect reflux even at a single valve level. Reflux may not become hemodynamically important until multiple valve sites become refluxive. The Doppler examination, therefore, can be considered a highly sensitive technique for detection of even early disease.

PPG.—Photoplethysmography was moderately sensitive when compared with descending venography or Doppler examination. Sensitivity was excellent when tested in patients with abnormal pressure measurements, but PPG had a uniformly low specificity, regardless of the reference standard used. A normal PPG test, therefore, generally signifies the absence of advanced reflux with pressure changes. The number of false-positive results in "normal" limbs is high, and this test may miss a number of limbs with minor forms of reflux.

Table 2.—Clinical Severity of Venous Insufficiency* and Associated Hemodynamics (Mean ± SD)

	PPG RT, s†	AVP† % Drop	AVP† RT, s	Valsalva-Induced FVP, mm Hg
Class				
I (n)	9.6 ± 4.2 (48)	36 ± 12 (23)	15 ± 3.4 (41)	4.9 ± 3.3 (35)
III (n)	7.0 ± 4.9 (84)	28 ± 9 (49)	10.5 ± 5.5 (68)	7.9 ± 4.9 (60)
P	NS	NS	<.002	<.1

*Classification by Venous Standards Committee.[4]

†PPG indicates photoplethysmography; RT, recovery time; AVP, ambulatory venous pressure; FVP, foot venous pressure.

For these reasons, perhaps it should not be used as the sole screening device in the vascular laboratory.

Ambulatory Venous Pressure Measurement.—The manual calf compression technique was compared with the traditional toe-stand technique in 44 limbs. No difference was seen in the mean recovery time (15 vs 15 seconds, respectively). Variations in mean postexercise pressure were less than 6 mm Hg (50 vs 56 mm Hg for manual compression and toe stands, respectively). The manual calf compression avoided difficulties with patient cooperation and eliminated exercise-induced reactive hyperemia, sometimes seen with the traditional toe-stand technique.

Compared with descending venography, ambulatory venous pressure (recovery times, <16 seconds) was 83% sensitive. Sensitivity of postexercise pressure drop (<50%) was slightly better. Ambulatory venous pressure was somewhat less sensitive when compared with venous Doppler examination, probably because reflux at multiple valve sites is required for the generation of abnormal ambulatory venous pressure. A small, but significant, percentage of patients with stasis ulceration have "normal" ambulatory venous pressure measurements.

Tourniquet Test to Differentiate Superficial from Deep Reflux.—In 14 limbs (11%) of 124, a below-the-knee tourniquet completely normalized ambulatory venous pressure recovery times, suggesting "pure" superficial disease. In 12 of these 14 limbs, descending venography was performed and showed reflux in the deep system.

In another group of limbs (n = 66), the tourniquet test showed significant (>3 seconds) improvement of ambulatory venous pressure recovery times in 18 limbs, suggesting combined superficial and deep disease. In 11 (61%) of these 18, combined disease was confirmed on descending venography. Superficial (saphenous) reflux was not found in the remaining seven limbs (39%) on descending venography. In 48 limbs, tourniquet application resulted in no change in ambulatory recovery times. However, 13 of these limbs had significant saphenous (and deep) reflux on descending venography, apparently missed by the tourniquet test (false-negative results of 27%). These data suggest that the tourniquet method may be unreliable in separating superficial from deep disease.

Valsalva-Induced Foot Venous Pressure.—The technique was highly reproducible. The coefficient of variation on repeated tests was 4% (n = 27). Mean (± SD) Valsalva-induced foot venous pressure in normal limbs was 2.9 ± 1.1 mm Hg (n = 24). In refluxive limbs, a mean value of 7.9 ± 5.1 mm Hg (n = 63) was obtained. This difference was significant ($P < .0001$). Patients with stasis symptoms undergoing valve reconstruction had somewhat higher values (9.2 ± 5.3 mm Hg, n = 41) which significantly improved after surgery (4.2 ± 2.5 mm Hg, n = 41; $P < .004$ vs preoperative values). The technique is highly sensitive in stasis ulceration (Table 1) and only 3% of the patients were asymptomatic in the presence of an abnormal test (n = 168). It was roughly similar to ambulatory venous pressure measurements in sensitivity and specificity values. However, the two techniques apparently define slightly different normal and abnormal populations. Each technique is abnormal only about two thirds (66% to 67%) of the time when the other technique is abnormal. A normal reading by each technique is obtained in only about three fourths (73% to 76%) of the limbs so tagged by the other technique (Table 1). This indicates that related, but different, values are being measured by the two pressure-based techniques.

Strip Test to Detect Valve Reflux During Surgery.—Only 89% of the patients determined to have reflux preoperatively by detailed studies, including the Doppler examination and descending venography, demonstrated valve insufficiency by the strip testing intraoperatively. In the other 11% of patients, the vein undergoes contraction from surgical manipulation. Contraction of the valve ring by this mechanism results in intraoperative valve competence.[6]

HEMODYNAMIC BASIS FOR CLINICAL GRADATION OF REFLUX

Table 2 shows the correlation between gradations of clinical severity (recommended by the Committee on Venous Standards[4]) and the corresponding PPG, Valsalva-induced foot venous pressure, the ambulatory venous pressure test results. Photoplethysmography, a qualitative test, shows little gradation with increasing clinical manifestation of disease. Such a gradation seems to be present with the other two pressure-based, semiquantitative techniques. Postexercise pressure drop (percentage) did not show a significant difference even though a suggestive trend was present. Despite the presence of an abnormal test indicating venous reflux, 8%, 13%, 5%, and 3% of limbs tested by Doppler, PPG, ambulatory venous pressure, and Valsalva foot venous pressure techniques, respectively, were clinically asymptomatic.

Ascending Venography: Calf Varicosities

The presence of calf varicosities on ascending venograms was often noted by the interpreting radiologist. The presence of calf varicosities (n = 77) was associated 100% with deep venous disease on descending venography. Seventy-four of 77 of these limbs also had ambulatory venous hypertension. *Therefore, calf varicosities are a sign of deep valve disease.*

Descending Venography

The sensitivity of descending venography in detecting valvular reflux was excellent when compared with other techniques, including direct observation (strip test) at the time of surgery (Table 1). Descending venography was also specific using the venous Doppler examination as the reference standard. Specificity of descending venography was low when ambulatory venous pressure or Valsalva-induced foot venous pressure was used as the reference. This is a reflection of the fact that descending venography is sensitive to even milder forms of venous reflux, whereas ambulatory venous pressure and Valsalva-induced foot venous pressure become abnormal only with more extensive disease.

The Horizontal Technique for Descending Venography

Descending venography when performed in the horizontal position as described by Thomas et al[9] was poorly sensitive (54%) with venous Doppler as the reference standard. The specificity was 89%. Because of the high false-negative rate (46%), it has since been abandoned.

Bilaterality

Reflux is predominantly bilateral. This is emphasized by the detection of bilaterality by various techniques, including descending venography (Table 3).

Superficial and Deep Venous Insufficiency

From descending venography, venous reflux can be identified as "pure," superficial (saphenous reflux only), pure deep reflux, or a combination (saphenous plus deep veins). The incidence of pure superficial reflux is diminutive (<1% [1/232]). Deep reflux either alone (71% [164/232]) or in combination with superficial reflux (29% [67/232]) was the predominant pathologic feature.

HEMODYNAMIC BASIS FOR GRADING REFLUX BY DESCENDING VENOGRAPHY

Reflux detected by descending venography was examined by two methods of classification: the Kistner classification[7] (based on the distal extent of reflux) and our classification[8] (based on the number of venous systems involved in reflux). Hemodynamic data and stasis ulcer incidence for these two systems of classification are given in Table 4. There is little correlation between hemodynamic values and the distal extent of reflux (Kistner classification). The other classification based on the number of venous systems involved in reflux was somewhat better in this regard; as more systems become refluxive, hemodynamic abnormality and stasis ulcer incidence correspondingly increased.

Table 3.—Incidence of Bilaterality of Venous Reflux

Technique Used as Reference*	n	% of Reflux Bilateral	 Unilateral
Descending venography	96	91	9
AVP RT	76	95	5
Valsalva-Induced FVP	54	85	15
Doppler	562	89	11

*AVP RT indicates ambulatory venous pressure recovery time, and FVP, foot venous pressure.

NUCLEOTIDE DESCENDING VENOGRAPHY

Nucleotide descending venography was originally introduced by us in the hope that the isobaric medium would eliminate artifactual reflux from downward streaming suspected to occur with hyperbaric contrast. The sensitivity and specificity of nucleotide descending venography were poor as compared with contrast descending venography or Doppler examination (Table 1). Nucleotide descending venography has also been abandoned.

COMMENT

As yet, there is no single "perfect" technique to assess venous reflux. The venous Doppler examination is, indeed, a reliable screening tool, but is qualitative and highly subjective. Even in experienced hands, reflux in closely proximate veins, such as the short saphenous and popliteal, may be confused with each other. Duplex scanners incorporating color-coded Doppler scans may solve most of these deficiencies. A scientific evaluation of this exciting new technique as compared with older techniques is awaited. Photoplethysmography has become popular because of its simplicity and totally noninvasive nature. However, it is moderately sensitive compared with descending venography and has a high false-positive rate compared with almost all other techniques in use.

Ambulatory venous pressure, even though considered the traditional "gold standard," cannot by itself differentiate obstruction from reflux or a combination of the two. In general, a correlation exists (Tables 2 and 4) between reflux hemodynamic disturbance and stasis changes in the skin. However, there is a wide range in these values and other factors, such as velocity of reflux, local tissue status, and variations in regional and local venous congestion, as suggested by Melville Williams, MD (oral communication, November 12, 1987), may be equally pertinent. In an analysis detailed elsewhere,[6] it was

Table 4.—Descending Venography: Classification and Associated Hemodynamics*

Classification	PPG/s	AVP With Tourniquet RT, s	 % Drop	Valsalva-Induced FVP	Stasis Ulcer Incidence, %
Venous system involved (n)					
Single level/single system	10.1 (25)	13.5 (20)	42.2 [1] (19)	3.4 [1] (14)	24 [1]
Single level/multiple system	10.3 (56)	14.1 (47)	34.9 [2] (44)	6.4 [2] (42)	52 [2]
Multiple level/multiple system	11.8 (105)	13.2 (85)	33.5 [3] (87)	6.3 [3] (7)	92 [3]
P	. . .	. . .	[1&2], [1&3]†	[1&2], [1&3]†	[1&2], [1&3]†
Kistner et al[7] classification, grade (n)					
1	8.1 [1] (24)	13.4 (17)	36.0 (18)	5.9 (16)	14
2	11.4 [2] (60)	14.1 (53)	38.0 (46)	6.2 (41)	41
3	11.5 [2] (60)	13.4 (54)	34.3 (50)	5.4 (39)	55
4	11.4 [2] (30)	11.6 (21)	34.7 (21)	7.7 (19)	27
P	[1&2]	NS	NS	NS	. . .

*PPG indicates photoplethysmography; AVP, ambulatory venous pressure; and FVP, foot venous pressure.
†Indicates significant.

shown that there was significant incidence of stasis ulceration even when postexercise pressures were below 50 mm Hg. Not surprisingly, the successful results of valve reconstruction have not correlated well with ambulatory venous pressure measurements postoperatively.[6]

Valsalva-induced foot venous pressure seems to correlate well with symptoms and seems to be especially sensitive to multivalvular venous reflux, which is most commonly associated with stasis ulceration.[6] It has proved to be a more reliable tool than ambulatory venous pressure for assessing the outcome of valve reconstruction surgery. Even though considerable overlap is present, Valsalva-induced foot venous pressure seems to define a population (both "normal" and "abnormal") somewhat different from ambulatory venous pressure measurement.

Descending venography has been practiced for some decades, but the technique has varied and has been subject to numerous artifactual and interpretational errors. Kistner et al[7] have standardized the technique and emphasized that reflux is significant only if it is present with the patient performing Valsalva's maneuver at a 60°-erect position. This point is amply underscored by our poor experience with the horizontal Valsalva technique for descending venography. The method described by Kistner et al seems to have eliminated most of the previous difficulties and is reliable if performed as they described. It is, however, deficient in infrafemoral disease in the presence of a competent femoral valve, as the dye is introduced into the system above the femoral valve. Thus, popliteal valve reflux below a functional femoral valve will be missed by this technique. Color-coded Doppler scan may be more precise in detecting such regional reflux. It remains to be seen whether the favorable expectations for this new modality are proved by the experience being gathered by many centers.

Nucleotide descending venography was introduced by one of us (S.R.)[10] in the hope of avoiding some of the streaming artifactual errors sometimes obtained with descending venography. It was expected that the isobaric nature of the nucleotide medium would avoid this difficulty. Because of unacceptably low sensitivity, the technique has been abandoned.

There is extensive literature on reflux venous insufficiency, some dating back to the early part of the century. Much of the case material invariably includes postthrombotic limbs with recanalization. Because reliable hemodynamic techniques to detect obstruction were not available, it seems highly likely the material consisted of a mixture of obstruction, reflux, and a combination. The material presented herein consists only of limbs with refluxive pathologic features. Examination of this material with multiple techniques, including liberal use of descending venography, allows the characterization of venous reflux in general terms. This perspective is different from the traditional view in several significant aspects. The major points may be summarized as follows: venous reflux is predominantly bilateral and the major etiological mechanism is cryptogenic in origin. Postthrombotic reflux is probably not the predominant cause and likely represents a minority of cases selected for pure reflux as outlined. Reflux overwhelmingly involves the deep system, which seems to be the basis for symptoms of pain, swelling, and ulceration. Combined superficial and deep reflux occurs in approximately one third of these patients (29% in this series). Isolated superficial (saphenous) venous reflux is distinctly uncommon, the incidence being less than 1% in this study. There seems to be a rough correlation between venous hypertension and stasis symptoms. There is a large SD, however, suggesting that factors other than venous hypertension play a part in the generation of symptoms. Patients with symptoms commonly have multiple valves at multiple levels involved in reflux (58% in this series). Even when reflux is confined to the thigh, stasis symptoms, including ulceration, can occur when multiple systems, ie, saphenous, superficial femoral, and profunda, become refluxive. The hemodynamic severity of reflux seems to correlate with the increasing number of venous systems that become refluxive. There is a high incidence (73%) of perforator incompetence in symptomatic limbs. Of these, 97% were of the secondary variety associated with deep valve reflux. Primary perforator incompetence could be identified in only 3% of these limbs. The presence of prominent calf varicosities noted on ascending venography usually accompanies the presence of deep valve reflux.

The small incidence of pure superficial reflux (confined to the saphenous system only) as determined by descending venography in this series is in stark contrast to the much higher incidence generally reported in the literature utilizing the tourniquet method to differentiate superficial from deep reflux. In our laboratory, there was poor correlation between the two techniques. Significant false-positive and false-negative results occurred when the tourniquet technique was compared with descending venography. This needs further clarification as this issue has important theoretical implications regarding the etiology of superficial varicosities and its relationship to deep venous reflux.

For screening purposes the venous Doppler examination (preferably Duplex scanner) seems to be superior to PPG. In symptomatic patients requiring therapy, pressure studies as outlined are indicated to assess hemodynamic severity and to rule out the presence of obstruction. All three of the described pressure studies (arm-foot venous pressure differential, ambulatory venous pressure, Valsalva-induced foot venous pressure elevations) can be carried out at a single sitting using the same venipuncture in the foot. Until the utility of Duplex scanners becomes more fully established, descending venography (Kistner's technique) remains the standard in assessing patients for valve reconstruction surgery.

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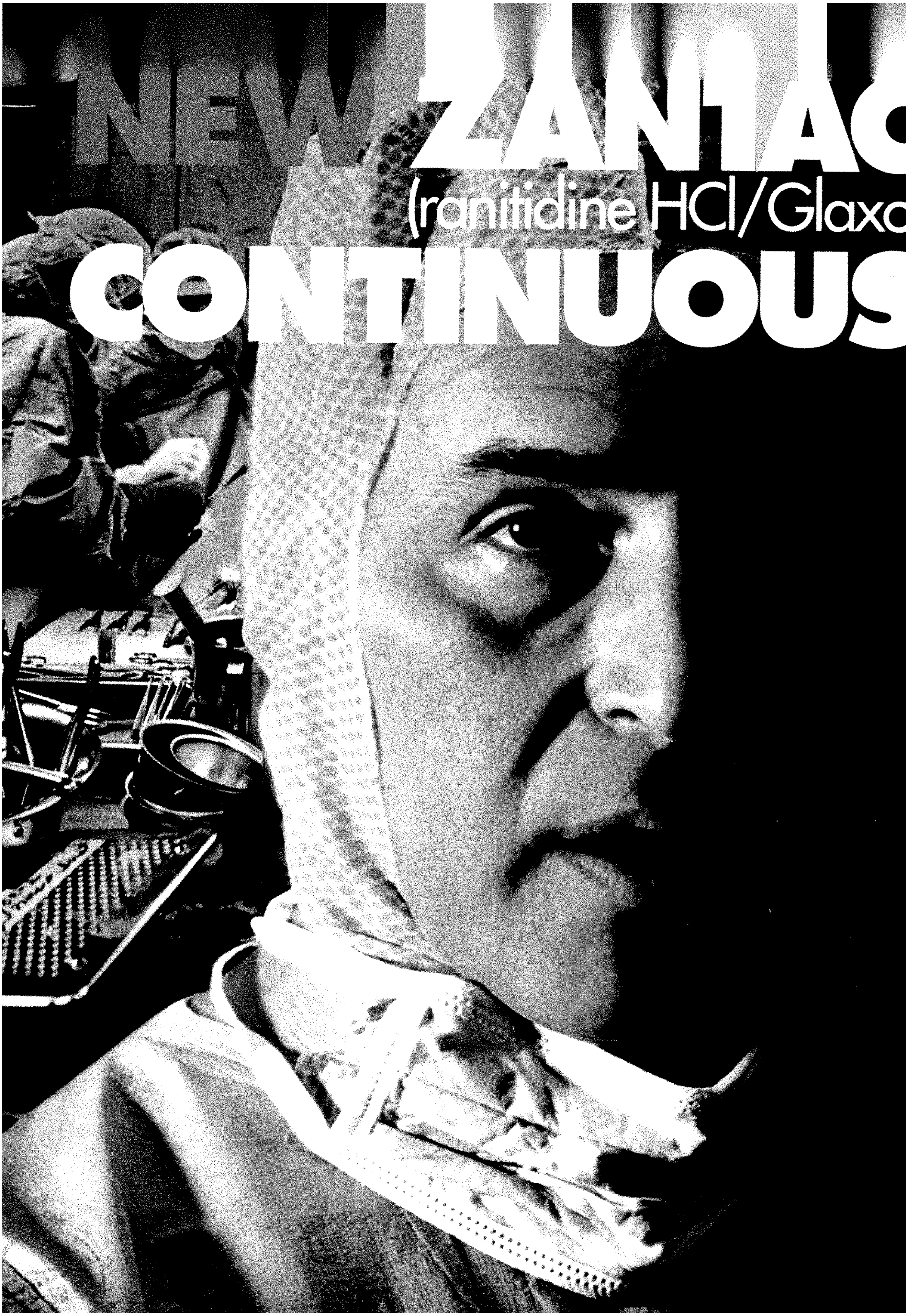
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* Please see complete Prescribing Information for indications.

† Rare cases of CNS effects, usually reversible, have been reported. Please see complete Prescribing Information for precautions.

Please see references and Brief Summary of Prescribing Information on next page.

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Zantac® Injection
(ranitidine hydrochloride)

BRIEF SUMMARY

Zantac® Injection Premixed
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® Injection/Zantac® Injection Premixed product labeling.

INDICATIONS AND USAGE: Zantac® Injection and Zantac® Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.

CONTRAINDICATIONS: Zantac® Injection and Zantac® Injection Premixed are contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.

2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended doses for five days or longer. Therefore, it seems prudent in patients receiving intravenous (IV) ranitidine at doses greater than or equal to 100 mg qid for periods of five days or longer to monitor SGPT daily (from day 5) for the remainder of IV therapy.

4. Bradycardia in association with rapid administration of Zantac® Injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded (see DOSAGE AND ADMINISTRATION).

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at oral doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits at oral doses up to 160 times the human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) treated with oral Zantac were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: Transient pain at the site of intramuscular injection has been reported. Transient local burning or itching has been reported with IV administration of Zantac®.

The following have been reported as events in clinical trials or in the routine management of patients treated with oral or parenteral Zantac. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, asystole, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® Injection/Zantac® Injection Premixed product labeling.)

Intramuscular Injection: 50 mg (2 ml) every six to eight hours. (No dilution necessary.)

Intermittent Intravenous Injection:

a. Intermittent Bolus: 50 mg (2 ml) every six to eight hours. Dilute Zantac Injection, 50 mg, in 0.9% Sodium Chloride or other compatible IV solution (see Stability) to a concentration no greater than 2.5 mg/ml (20 ml). Inject at a rate no greater than 4 ml per minute (five minutes).

b. Intermittent Infusion: 50 mg (2 ml) every six to eight hours. Dilute Zantac Injection, 50 mg, in 5% Dextrose Injection or other compatible IV solution to a concentration no greater than 0.5 mg/ml (100 ml). Infuse at a rate no greater than 5 to 7 ml per minute (15 to 20 minutes).

Zantac Injection Premixed solution, 50 mg, in 0.45% Sodium Chloride, 100 ml, requires no dilution and should be infused over 15 to 20 minutes.

In some patients it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of the dose, but generally should not exceed 400 mg per day.

Continuous Intravenous Infusion: Add Zantac Injection to 5% Dextrose Injection or other compatible IV solution. Deliver at a rate of 6.25 mg per hour (eg, 150 mg [6 ml] Zantac Injection in 250 ml of 5% Dextrose Injection at 10.7 ml per hour).

For Zollinger-Ellison patients, dilute Zantac Injection in 5% Dextrose Injection or other compatible intravenous solution to a concentration no greater than 2.5 mg/ml. Start the infusion at a rate of 1.0 mg/kg/h. If after four hours either a measured gastric acid output is greater than 10 mEq/h or the patient becomes symptomatic, the dose should be adjusted upwards in 0.5-mg/kg/h increments, and the acid output should be remeasured. Doses up to 2.5 mg/kg/h and infusion rates as high as 220 mg/h have been used.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 50 mg every 18 to 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® Injection, 25 mg/ml, containing phenol 0.5% as preservative, is available as follows:
NDC 0173-0362-38 2-ml single-dose vials (Tray of 10)
NDC 0173-0363-39 10-ml multi-dose vials (Singles)
NDC 0173-0363-00 40-ml Pharmacy Bulk Packages (Singles)
NDC 0173-0362-00 2-ml single-dose, prefilled, disposable syringes (Singles)

Store below 30° C (86° F). Protect from light. Store 40-ml vial in carton until time of use.

Zantac® Injection Premixed in 0.45% Sodium Chloride, 0.5 mg/ml, is available as a sterile, premixed solution for IV administration in 100-ml, single-dose, flexible plastic containers (NDC 0173-0407-00). It contains no preservatives.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25° C); however, brief exposure up to 40° C does not adversely affect the product.

August 1990

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.

Zantac® Injection in vials:
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Zantac® Injection in prefilled syringes:
Manufactured for Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
by Survival Technology, Inc., Bethesda, MD 20814
Zantac® Injection Premixed:
Manufactured for Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
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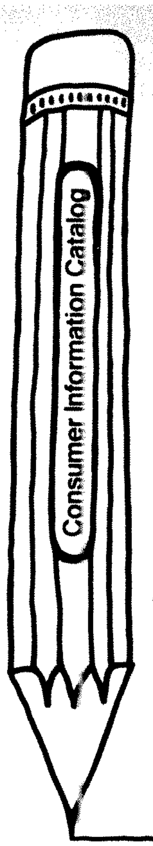

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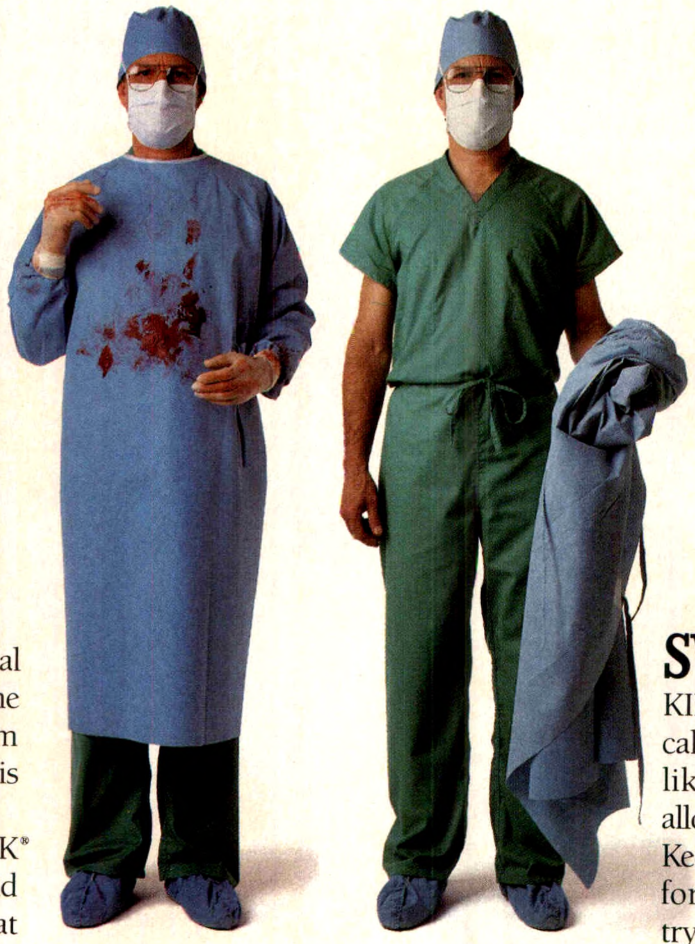

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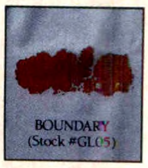

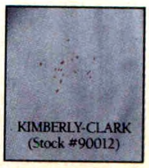

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Kimberly-Clark

Does Survival Depend on the Amount of Autotransplanted Splenic Tissue?

M. H. Shokouh-Amiri, MD; S. Rahimi-Saber, MD; C. Palnaes Hansen, MD;
P. Skov Olsen, MD, PhD; S. Lindkaedr Jensen, MD, PhD

• Susceptibility to *Streptococcus pneumoniae* infection was studied in 11 groups of rats allocated to sham operation, splenectomy, or splenic autotransplantation of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the removed spleen. Three months later, all rats were exposed intravenously to type 1 *Streptococcus* pneumoniae (median lethal dose, LD50, for control group). Survivors were killed 13 days after the bacterial challenge. Autopsy showed that more splenic tissue was recovered in rats that received less than 50% splenic tissue compared with those that received 50% or more. More survivors were found among sham-operated rats (47.5%; 95% confidence intervals, 32 to 68) and rats that had 40% splenic tissue implanted (35%; confidence interval, 20 to 54) or those that were found to have regenerated 40% splenic tissue. We conclude that 40% of the spleen should be autotransplanted to protect the rat optimally against infection after splenectomy.

(*Arch Surg.* 1990;125:1472-1474)

It is well known that the normal spleen protects the organism against infection and that splenectomy is associated with an increased incidence of postsplenectomy infections.[1-3] Therefore, the management of splenic trauma has changed toward splenic preservation techniques.[4-9] However, if the spleen is completely shattered, preservation is very difficult, or most often, impossible and the spleen has to be removed. To avoid postsplenectomy infection, autotransplantation of the damaged splenic tissue has been recommended.[10-14] Despite this, there is still controversy over how much splenic tissue is necessary to transplant to protect the organism optimally against bacterial infection. To shed further light on this interesting and important issue, the present study was undertaken in splenectomized rats submitted to a bacterial challenge 3 months after autotransplantation of various amounts of splenic tissue.

MATERIALS AND METHODS

Animals and Operative Procedures

Male Wistar rats weighing 350 to 450 g were used. The rats were brought to the laboratory 1 week prior to operation in groups of 40. A total of 440 rats were used. They were fed with a standard rat food and free access to water. They ate no food for 12 hours before surgery but had free access to water. The rats were anesthetized with intraperitoneal sodium pentobarbital (5 mg per 100 g of body weight). Laparotomy was performed through a midline incision. The abdomen was carefully searched for the presence of any accessory splenic tissue. One of the following procedures was performed: (1) mobilization of the spleen only (sham operation) (n = 40); (2) total splenectomy (n = 40); (3) total splenectomy followed by autotransplantation in groups of 40 rats of respectively 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the weight of the intact spleen. The spleen was removed and weighed (Mettler H 20 P, Metter-Tolido-AG, Greifensee, Switzerland). The spleen was cut into thin slices of 1 mm thickness. Enough of the splenic tissue slices corresponding to the allocated percentage of each group were spread evenly over the omentum, which was wrapped over the implanted tissue, and the pouch was closed by 4-0 interrupted sutures. Splenic slices were spread over omentum rather far from each other in group 3, 4, 5, and 6, while

Table 1

	Sham-operated	Total Splenectomy
No. of rats submitted to bacterial challenge	40	39
Median weight of autotransplanted splenic tissue, mg (range)	1045 (945-1134)	0
Survived, No. (%)	19 (47.5)	0
Mean survival time, h (range)	47.2 (18-106)	41.6 (12-73)

Table 2.

	Sham-operated
No. of rats submitted to bacterial challenge	40
Median weight of splenic tissue found at autopsy, mg (range)	1106 (1000-1270)
Survived, No. (%)	19 (47.5)
Mean survival time, h (range)	47.2 (18-106)

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From the Department of Surgical Gastroenterology, Rigshospitalet, University of Copenhagen (Drs Shokouh-Amiri, Rahimi-Saber, Hansen, and Olsen); and the Department of Surgical Gastroenterology, Aarhus Kommunehospital, University of Aarhus (Dr Jensen), Denmark.

Reprint requests to Department of Surgery, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark (Dr Shokouh-Amiri).

the distance between tissue slices in the omental pouch decreased as more and more splenic tissue was placed in the omental pouch in groups 7, 8, 9, 10, and 11.

Three months after operation, a second laparotomy was performed and 1.7×10^3 colony forming units (CFUs) of type 1 *Streptococcus pneumoniae* were injected into the inferior vena cava. After the bacterial challenge, the rats were observed closely. Moribund rats were laparotomized under light anesthesia and the splenic remnants were removed and weighed.

Thirteen days after the bacterial challenge, the surviving animals were subjected to a third laparotomy. The recovered splenic tissue was weighed. Dead animals were autopsied and the weight of surviving splenic tissue was recorded as well as any gross pathologic findings. All operations were performed under sterile conditions.

Bacteriology

Type 1 *S pneumoniae* of the same clinical isolate was used in all experiments. We found in a pilot study that an inoculum of 1.7×10^3 (1.31 to 2.23×10^3) CFUs was the median lethal dose, LD50, in a group of 30 healthy Wistar male rats weighing 350 to 450 g. For the preparation of the batches of inocula, the strain was cultured in Todd-Hewitt broth and on the following day, passed twice in fresh serum broth (one part of fetal calf serum and five parts of Todd-Hewitt broth). The following steps describes the standardization of the early logarithmic growth phase of the inoculum. The broth culture was centrifuged at 3000*g* for 15 minutes, the pellets suspended in fresh serum broth to an optical density of 0.30 at 540 nm (model 252 Corning Colorimeter, Corning Ltd, Halstead, Essex, England) and measured with fresh serum broth as control. This tube was incubated in a water bath at 30°C for approximately 3 hours until an optical density of 0.62 was reached. The final inoculum was prepared after appropriate dilution in fresh serum broth. Viable counts were determined by subsequent inoculation of 100-μL samples as a double trial on 5% blood agar plates. Since the virulence of pneumococci is closely related to the presence of adequate polysaccharide in the capsule, each batch of inocula was tested with type 1 pneumococcal antiserum (Neufeldt's capsule swelling reaction). Separate samples of inocula for each animal were quickly prepared, using 1-mL aliquots containing 1.7×10^3 CFUs frozen in acetone and dry ice and stored at −80°C. Immediately before use, the tubes were rapidly thawed by holding in the hand. No changes in viability were observed after storage for at least 6 months. A similar technique has been described by Alwmark et al.[15]

Statistical Analysis

The Mann-Whitney *U* test was used to compare the different groups with regard to differences in splenic weights. The χ^2 test was used to compare the number of survivors in each treatment group. *P* values of less then .05 were considered significant.

RESULTS

The median weight of the spleen in all 440 rats was 1040 mg (range, 905 to 1235 mg) and it did not differ significantly from the median weights of the spleens in the different treatment groups. A positive correlation ($r = .483$) between the weights of implanted and recovered tissues was found. However, this correlation was lost when the weight of implanted tissue exceeded 50% of the weight of the intact spleen ($r = .9182$; $P < .01$). Table 1 shows the median weights of implanted splenic tissue in the different treatment groups and the number of rats and survivors after the bacterial challenge in each group. The survival time for rats that failed the bacterial challenge is also demonstrated in Table 1. The number of survivors in the group implanted with 40% of the weight of the intact spleen was significantly greater than the number in any of the other treatment groups ($P < .05$ for all groups), whereas the difference was not statistically significant between the 40% group and the sham-operated group (32.5% vs 47.5%).

Table 2 shows the number of survivors related to the amount of splenic tissue found at autopsy. It should be noted that there were significantly more survivors in the group that had splenic tissues corresponding to 40% (about 400 mg) of the weight of intact spleen left at autopsy compared with all other groups ($P < .05$ for each group) except the sham-operated group (35% [CI, 20-54] vs 47.5% [CI, 32-68]).

Autopsy revealed significantly more abscesses in the omental pouches of rats receiving more than 50% splenic tissue

Weight of Implanted Splenic Tissue and the Result of Bacterial Challenge*

Amount of Splenic Tissue Transplanted								
(10%)	(20%)	(30%)	(40%)	(50%)	(60%)	(70%)	(80%)	(90%)
38	33	30	37	35	33	33	34	30
111 (92-116)	217 (194-222)	285 (280-305)	433 (402-440)	501 (493-508)	609 (595-612)	731 (711-740)	826 (814-835)	918 (900-923)
0	1 (3)	5 (16.6)	12 (32.5)	3 (8.5)	4 (12)	1 (3)	1 (2.9)	0
45.6 (30-144)	51.3 (20-65)	57.3 (34-111)	81.76 (5-240)	44.6 (4-73)	52.2 (24-100)	58 (4-155)	50 (20-81)	68.8 (26-150)

*The rats were exposed to 1.7×10^3 colony forming units of type 1 *Streptococcus pneumoniae* intravenously and grouped according to the amount of the splenic tissue transplanted.

Weight of Retained Splenic Tissue and the Result of Bacterial Challenge*

Amount of Retained Splenic Tissue After Autotransplantation									
(0%)	(10%)	(20%)	(30%)	(40%)	(50%)	(60%)	(70%)	(80%)	(90%)
60	64	58	51	38	31	15	11	14	0
0	108 (45-137)	205 (152-245)	297 (260-320)	415 (252-440)	494 (665-545)	602 (550-625)	702 (655-745)	784 (765-798)	0
0	0	3 (5.3)	6 (11.7)	13 (35)	4 (13)	1 (6.6)	0	0	0
48.2 (12-155)	43.2 (4-144)	46.5 (5-160)	55 (5-111)	70.6 (20-240)	48.5 (20-73)	65 (24-155)	75 (40-150)	65 (33-150)	0

*The rats were exposed to 1.7×10^3 colony forming units of type 1 *Streptococcus pneumoniae* intravenously and grouped according to the amount of the retained splenic tissue after autotransplantation.

compared with rats receiving less than 50% (13.8% [CI, 8 to 21] vs 3.6% [CI, 1 to 8]; $P<.05$).

COMMENT

These results demonstrated that survival was significantly higher in rats transplanted with a splenic tissue corresponding to 40% of the weight of the intact spleen compared with other percentages of the weight of the intact spleen. It was also demonstrated that a positive correlation exists between weights of implanted and recovered tissues until the weight of the implanted splenic tissue exceeds the weight of the intact spleen by 50%. To overcome the threat of overwhelming postsplenectomy infection with its high mortality,[16] autotransplantation of splenic tissue has been recommended since prophylactic polyvalent pneumococcal vaccination or long-term antibiotic treatment does not provide complete protection against infection. Several important questions of interest concerning splenic autotransplantation are still unanswered despite the huge amount of experimental work on this subject from all over the world. For example, what amount of splenic tissue should be implanted to protect the organism optimally against postsplenectomy infection? Until now, definitive studies on this important question have been lacking.

It has been claimed that the more splenic tissue that is transplanted, the more tissue will survive, and the greater will be the immunologic function.[17] If we define immunologic function as the ability of an animal to survive a bacterial challenge after a splenectomy and the splenic autotransplantation, our study cannot support this claim. In contrast, we have demonstrated that increasing splenic mass does not yield proportionally improved immunologic function. According to our study, in which we were able to determine the minimum as well as the maximum amount of splenic tissue that provides optimal immunologic function, 40% of the weight of the intact spleen gave the best result. A decrease or an increase in transplanted or surviving splenic tissue worsened the immunologic function significantly.

Theoretically, the most important determining factors for optimal immunological function of the spleen are an intact circulation[18] and a normal architecture. However, it is controversial whether the regenerated splenic tissue has an architecture similar to the normal spleen.[19,20] It is also unknown whether the amount of implanted tissue is of importance for the histologic appearance of the regenerated tissue. In theory, it could be that approximately 40% of the weight of the intact spleen induces a regenerative process that results in an architecture similar to that of the normal spleen due to a better circulation establishment from the capillaries of the omentum. We are now undertaking histological examination of the present material, which may answer this question.

The reasons for the better immunological function in animals autotransplanted with 40% splenic tissue could be a better phagocytic function, a better ability to produce immunoglobulins, and a better clearance of bacteria from the circulation. Similar studies have to be performed in higher vertebrates (closer to human) to find out the best possible method of giving the optimal regeneration of autotransplanted splenic tissue before embarking on clinical trials.

We are grateful to J. Henrichsen, MD, PhD, of Statens Seruminstitut, Copenhagen for supplying the strains, and Ulla Steen Petersen and Inge Bente Madsen for technical and secretarial assistance.

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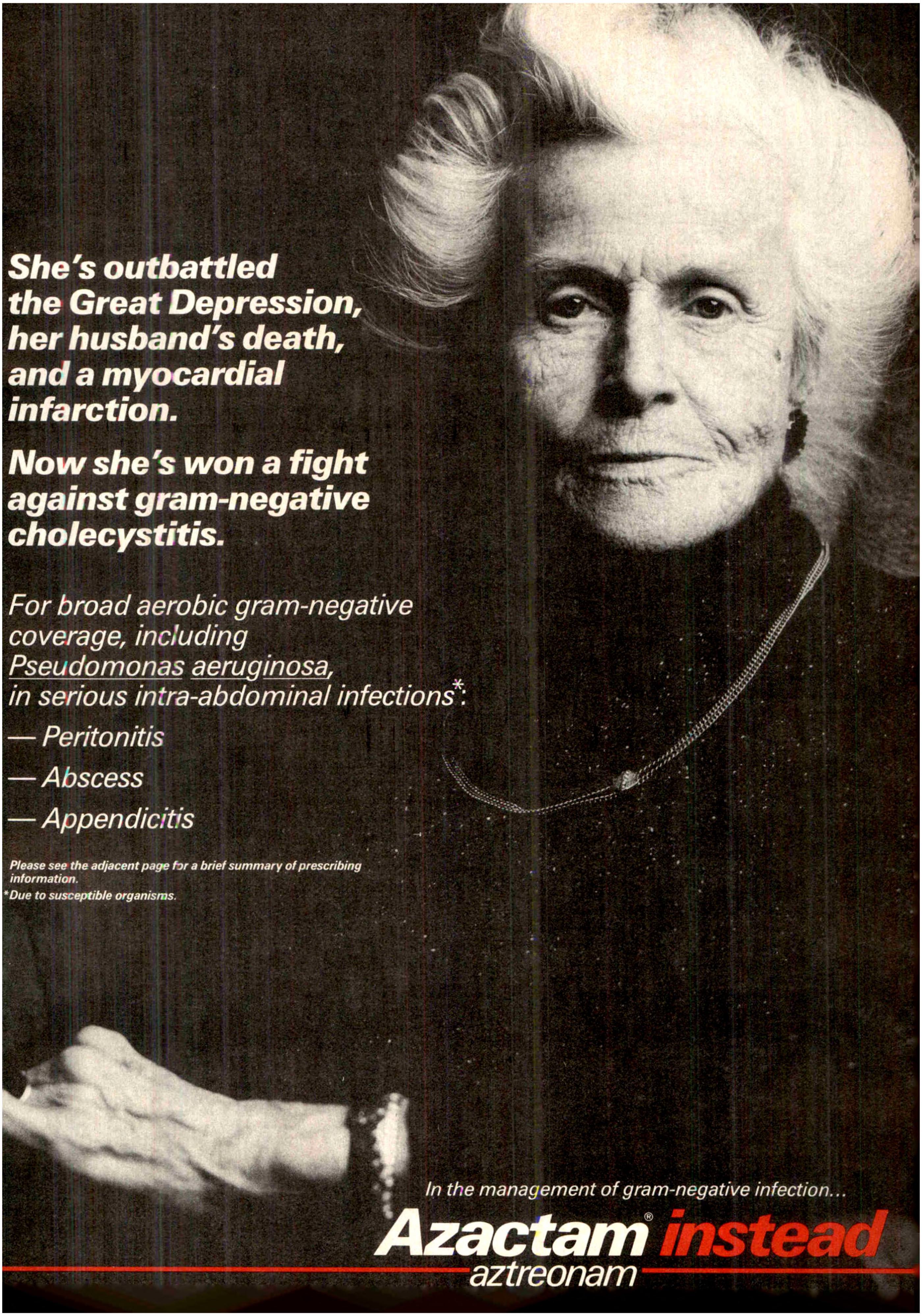

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DESCRIPTION—AZACTAM (aztreonam, Squibb) is the first member of a new class of antibiotics classified as monobactams. AZACTAM is a totally synthetic bactericidal antibiotic with activity against a wide spectrum of gram-negative aerobic pathogens. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics.

AZACTAM For Injection is a sterile, nonpyrogenic, sodium-free, white to yellowish-white lyophilized cake, containing approximately 780 mg arginine per gram of aztreonam for intramuscular or intravenous use following constitution. Aqueous solutions of the product have a pH in the range of 4.5-7.5.

INDICATIONS AND USAGE—Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of the susceptibility testing are available; subsequently, appropriate antibiotic therapy should be continued.

AZACTAM For Injection is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: **Urinary Tract Infections** (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella oxytoca*, Citrobacter* species* and *Serratia marcescens**. **Lower Respiratory Tract Infections,** including pneumonia and bronchitis caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae, Proteus mirabilis, Enterobacter* species and *Serratia marcescens**. **Septicemia** caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis*, Serratia marcescens** and *Enterobacter* species. **Skin and Skin-Structure Infections,** including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli, Proteus mirabilis, Serratia marcescens, Enterobacter* species, *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Citrobacter* species*. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli, Klebsiella* species, including *K. pneumoniae, Enterobacter* species including *E. cloacae*, Pseudomonas aeruginosa, Citrobacter* species* including *C. freundii** and *Serratia* species* including *S. marcescens**. **Gynecologic Infections,** including endometritis and pelvic cellulitis caused by *Escherichia coli, Klebsiella pneumoniae*, Enterobacter* species* including *E. cloacae**, and *Proteus mirabilis**.

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

Concurrent Therapy—Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected, therapy should be initiated using an antianaerobic agent concurrently with AZACTAM. Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing, appropriate antibiotic therapy should be continued.

CONTRAINDICATION—Aztreonam is contraindicated in patients with known allergy to this antibiotic.

WARNINGS—Careful inquiry should be made for a history of hypersensitivity reaction to any antibiotic or other drugs. Antibiotics should be given with caution to any patient who has had some form of allergy, particularly to drugs. It is recommended that patients who have had immediate hypersensitivity reactions (e.g., anaphylactic or urticarial) to penicillins and/or cephalosporins should be followed with special care. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures.

PRECAUTIONS—General: In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy. If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenicity studies in animals have not been performed. Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level. Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

Pregnancy—Pregnancy Category B: Aztreonam crosses the placenta and enters the fetal circulation. Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Nursing Mothers—Aztreonam is excreted in breast milk in concentrations that are less than 1% of concentrations determined in simultaneously obtained maternal serum consideration should be given to temporary discontinuation of nursing and use of formula feedings.

Pediatric Use—Safety and effectiveness have not been established in infants and children.

ADVERSE REACTIONS—Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9% and 2.4%, respectively. Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3% include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity: *Hypersensitivity*—anaphylaxis. *Hematologic*—pancytopenia, neutropenia, thrombocytopenia, anemia, leukocytosis, thrombocytosis. *Gastrointestinal*— abdominal cramps; rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. *Dermatologic*—purpura, erythema multiforme, urticaria, exfoliative dermatitis, petechiae, pruritus, diaphoresis. *Cardiovascular*—hypotension, transient ECG changes (ventricular bigeminy and PVC). *Respiratory*—one patient experienced flushing, chest pain, and dyspnea. *Hepatobiliary*—hepatitis, jaundice. *Nervous System*—seizure, confusion, vertigo, paresthesia, insomnia, dizziness. *Musculoskeletal*—muscular aches. *Special Senses*—tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing and nasal congestion, halitosis. *Other*—vaginal candidiasis, vaginitis, breast tenderness. *Body as a Whole*—weakness, headache, fever, malaise.

Adverse Laboratory Changes—Those reported without regard to drug relationship during clinical trials were: *Hepatic*—elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1% of recipients (see above). *Hemic*—increases in prothrombin and partial thromboplastin times, eosinophilia, positive Coombs test. *Renal*—increases in serum creatinine.

OVERDOSAGE—If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

DOSAGE AND ADMINISTRATION—Dosage adjustments are recommended for patients with impaired renal function. In elderly patients, estimates of creatinine clearance should be obtained and appropriate dosage modifications made if necessary.

HOW SUPPLIED—AZACTAM For Injection (Aztreonam For Injection)—Lyophilized—is supplied in single-dose 15 mL vials containing **500 mg,** or **1 g**/vial; in single-dose 30 mL vials containing **2 g**/vial; and in single-dose 100 mL intravenous infusion bottles containing **500 mg** or **1 g** or **2 g**/bottle.

Consult package insert before prescribing AZACTAM (aztreonam).

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*Efficacy for this organism in this organ system was studied in fewer than ten infections.

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Primary Malignant Peritoneal Mesothelioma

A Report of Seven Cases and a Review of the Literature

Juan A. Asensio, MD; Peter Goldblatt, MD; Neil R. Thomford, MD

• Mesothelioma of the peritoneum is a rare malignant neoplasm easily mistaken by both surgeon and pathologist for one of the more common neoplasms of the abdomen. Review of our records from metropolitan-area hospitals for the past 15 years identified seven patients with primary peritoneal mesotheliomas. Their diagnosis, management, and survival is analyzed. We report a case of an extended survivor (7 years) and one of a long-term survivor (15 years), as well as what we believe to be the only case in the literature presenting with a coexistent malignant neoplasm. Prevention of this commonly fatal neoplasm is linked to avoiding occupational exposure to asbestos; long-term survival for a few patients may be achieved with correct identification of the neoplasm and aggressive management. This report includes a review of the literature.

(*Arch Surg.* 1990;125:1477-1481)

Malignant mesothelioma of all primary sites is an uncommon neoplasm with only 2.2 cases per million per year reported in the United States.[1] The recent unusual interest in the disease is the result of the identification of asbestos as a probable causative agent. Most mesotheliomas are of pleural origin. The Eastern Cooperative Oncology Group reported a total of 104 cases of which only 7 cases were primary peritoneal mesotheliomas.[2] Mesotheliomas of the abdomen were first described in 1908 in a report by Miller and Wynn.[3] This report described 7 cases and documented the varied clinical presentation and course of these highly malignant tumors.

Malignant mesotheliomas are diffuse tumors arising from the mesothelial cell.[4-6] The surface linings of three serosal cavities (pleura, peritoneum, and pericardium) are the major sites of origin. Peritoneal mesotheliomas appear as hard, whitish nodules scattered over the peritoneal surfaces. These nodules later coalesce to form plaques or masses, extending into the surrounding tissues. Serosal spread to organs is common but there is limited invasion of the bowel and liver.[5-7,9] Metastases are usually to regional lymph nodes or possibly the thoracic cavity.

First classified by Whitwell and Rawcliffe,[10] malignant mesotheliomas are divided into three different subtypes: epithelial form, biphasic (mixed) form, and fibrous form. In the epithelial form, neoplastic cells may show various arrangements. Papillary, tubular, tubulopapillary, or any combination of these patterns may be present in a single case.[6-8] In the biphasic (mixed) form, neoplastic cells are of two types: mesenchymal and epithelial cells with intermediate transitional cells.[6-8] Neoplastic cells in the fibrous form are spindle shaped in parallel arrangement and the neoplasm may be indistinguishable from a fibrosarcoma on histologic examination alone. The large majority of the peritoneal mesotheliomas are either of the epithelial form (tubulopapillary) or the mixed form. They are rarely of the fibrous form, which is most often of pleural origin (Figs 1 and 2).[6-8]

PATIENTS AND METHODS

The records of all patients with a diagnosis of mesothelioma admitted to hospitals within metropolitan Toledo, Ohio, during the 15-year period ending December 31, 1988, were reviewed. Patients with evidence of thoracic mesothelioma were excluded. Seven cases of primary abdominal mesothelioma were identified and confirmed by study of histologic sections of specimens of each tumor. There were three men and four women ranging in age from 39 to 66 years. The mean age at the time of diagnosis for each sex was 57 years.

Presenting symptoms included abdominal pain (six cases), abdominal distention (five cases), nausea and vomiting (three cases), and diarrhea (four cases). Only one patient had prolonged exposure to asbestos. One patient had a medical history of coexisting malignant neoplasm (transitional cell carcinoma of the bladder). Abnormal physical findings included ascites (five patients) and an abdominal mass (two patients). No patient had symptoms or signs of pulmonary diseases. The chest roentgenograms of all seven patients were interpreted as normal. Results of common blood and urine studies did not show any consistent abnormalities.

The diagnosis was established by laparotomy in six cases and by autopsy in one instance. In all seven patients, cytology of ascitic fluid obtained preoperatively, intraoperatively, or at postmortem examination was diagnostic of mesothelioma. The types of mesothelioma were epithelial in six cases (tubulopapillary in one case, papillary in five cases) and biphasic mixed form in the remaining case.

Five patients had biopsy or partial excision of the mesothelioma with subsequent administration of adjuvant chemotherapy. The chemotherapeutic regimens used included doxorubicin and cyclophosphamide (three cases); doxorubicin alone (one case); doxorubicin,

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dimethyl-triazenoimidazole carboximide, melphalan, and fluorouracil (one case). Four of the five patients died within 1 year; the mean survival was 5 months. The fifth patient, treated with doxorubicin alone, survived 7 years after the diagnosis. Two years after the diagnosis was made, a peritoneojugular venous shunt was inserted to manage his ascites. Five years after the discovery of his mesothelioma, he underwent repair of bilateral inguinal hernias, at which time the hernia sacs removed from both inguinal areas revealed mesothelioma.

The sixth patient had total excision of the mesothelioma with recurrence and reexcision 7 years later. She remains well 15 years after the initial diagnosis and 7 years after reexcision of the tumor. This patient did not receive chemotherapy after either operation. The mesothelioma of the seventh patient was not discovered until autopsy.

REVIEW OF THE LITERATURE

Malignant mesothelioma is a rare disease. Only 2.2 cases per million are reported per year in the United States.[1] Only 20% to 40% of malignant mesotheliomas arise from the peritoneum.[11,12] Most reports in the literature list a combined incidence of pleural and peritoneal mesothelioma. The State of New York Bureau of Environmental Epidemiology and Occupational Health[12] reported an incidence for peritoneal mesotheliomas of 0.9 per million population in a study of 285 patients. Moertel[8] reported the annual Canadian incidence of peritoneal mesothelioma at 1 case per million population per year and has collected 169 cases from the literature. The tumor is very rare in children.[13-16] A recent combined review from the universities of Chicago and Minnesota reported only 41 cases in patients below the age of 16 years.[15]

Epidemiological studies link occurrence of mesotheliomas with environmental factors and carcinogens. The association between mesotheliomas and asbestos exposure was first reported by Wagner et al[17] in 1960. In the majority of the cases reported in the literature, there is a clear history of exposure of the patient or close relatives to asbestos, or the patient has lived in close proximity to areas of intense asbestos usage. The causative link to asbestos is not as well established in children.[2,5,6,8,12,13,15,18-26]

There is a male predominance in both the adult and the pediatric population, suggesting modulating etiologic factors other than occupational exposure. The median age at the time of diagnosis is 54 years. The age range in which the tumor has been reported is 2 to 92 years; however, 63% of the cases occurred between ages 45 and 64 years.*

The clinical presentation is usually nonspecific. There is a relatively short interval of significant symptoms. The most frequent initial symptom is nonspecific abdominal pain, which is often epigastric or in the right upper quadrant. Other symptoms include signs of bowel obstruction, such as cramps, nausea and vomiting, malaise, fever, abdominal enlargement, occasional dyspnea, anorexia, marked weight loss, and diarrhea. Ascites is the most common physical sign, occurring in 90% of the patients. Other common findings are the presence of an abdominal, extrarectal, or pelvic mass; anemia; and hypoglycemia.

Primary malignant abdominal mesotheliomas have been reported in a variety of anatomical locations, resulting in some rather unusual clinical presentations. They have been described in the tunica vaginalis hernia sacs[31,32] and in the tunica vaginalis propria testis (spermatic cord hydroceles).[33-42] They have presented as pelvic and adnexal masses simulating gynecologic tumors,[43,44] as an umbilical tumor[45] or retroperitoneal tumors,[46] and as isolated lesions of the small intestine.[47] They also have been reported to occur simultaneously in both pleural and peritoneal locations.[7,27,48-51]

Unusual clinical presentations include cases presenting as an acute surgical abdomen,[22] a partial small-bowel obstruction,[21] and with symptoms suggesting acute testicular torsion.[36] Other presentations have included diffuse abdominal ossification,[52] and diffuse liposclerotic mesenteritis.[53] They have been reported in a male pseudohermaphrodite with asymmetrical gonadal dysgenesis[54] and in association with hypoglycemia.[20,55,56] Finally, there are isolated reports of mesotheliomas developing after the administration of radiation therapy for seminoma of the testis,[57] carcinoma of the cervix,[58] and after the administration of thorium dioxide (Thorotrast).[59]

Peritoneal mesotheliomas have been reported to secrete a variety of ectopic hormones including antidiuretic hormone,[60] growth hormone,[56,61] corticotropin,[62] and insulinlike substances.[25] They have been associated with thrombocytosis,[28,63] polyclonal hyperimmunoglobulinemia,[64] and increased production of fibrin degradation products.[28]

In a large autopsy series, it was determined that local invasion and metastases were common and that peritoneal mesotheliomas were more likely to spread than tumors of other histogenesis showing comparable serous membrane involvement.[65] In that series of 28 cases, local invasion of the gastrointestinal tract occurred in 22 cases (extending to the submucosa and mucosa in 9 cases); the abdominal wall (6 cases); the liver parenchyma, diaphragm, and retroperitoneum (5 cases each); and the bladder and pancreas (2 cases each). Metastasis occurred to lymph nodes, viscera, and both viscera and lymph nodes (6 cases each). Other organs involved by metastases included the liver (8 cases), lung (5 cases), pleura (6 cases), pericardium (2 cases), and the heart and adrenal glands (1 case each).

The diagnosis of primary malignant abdominal mesothelioma is difficult because it is an uncommon disease and the symptoms and clinical presentation are so varied and nonspecific. A high index of suspicion coupled with a positive history of asbestos exposure may suggest the diagnosis.

In the past, most diagnoses were made at autopsy[28]; however, due to the increase in physician awareness, diagnoses are now being made ante mortem with an increasing frequency.[9,19,22,29,44,56] No test other than biopsy and histologic study is specific for the diagnosis.

Although no specific roentgenographic findings are associated with peritoneal mesotheliomas, ascites is common, and peritoneal mesotheliomas have been reported presenting as strictures in the transverse colon and the proximal small bowel[67] and with small-bowel obstruction.[21] Roentgenological findings that should raise the question of peritoneal mesothelioma in patients with an industrial history of asbestos exposure include the following[68]: (1) evidence of small- or large-bowel obstruction with or without ascites; (2) soft-tissue masses causing displacement of intra-abdominal structures; and (3) contrast studies showing a diffuse extrinsic indentation of the bowel with submucosal infiltration and encapsulation.

A recent study investigating the computed tomographic scan appearance of histologically proved malignant abdominal mesotheliomas concluded that the findings of diffuse mesenteric and peritoneal involvement and ascites should suggest the diagnosis.[69] This study further concluded that computed tomography may be useful in identifying promising biopsy sites and in monitoring the response to therapy.[69] Angiographic studies of peritoneal mesotheliomas show mildly or moderately hypervascular lesions without arteriovenous shunting or arterial encasement, and are predominantly fed by right and left gastroepiploic arteries.[70]

Two studies[71,72] describe the ultrasonographic findings of malignant peritoneal mesotheliomas that include abnormal echogenic tumor patterns within the distribution of the omen-

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* References 5, 6, 8, 9, 13, 19-21, 23, 25-30.

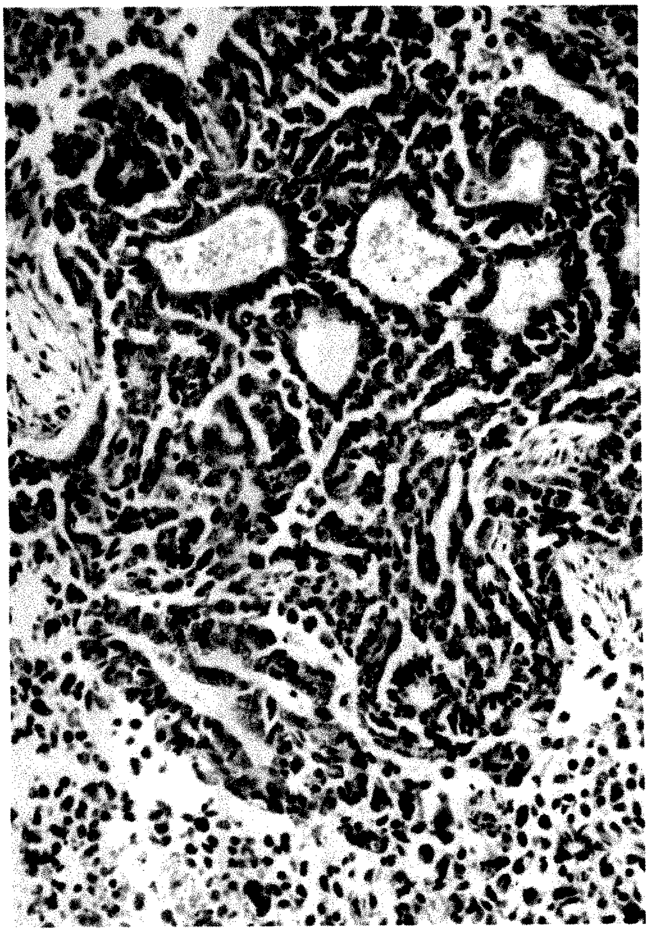

Fig 1.—Pseudoglandular pattern in a primary malignant peritoneal mesothelioma. Papillary appearance is seen at lower left. This tumor showed a mixed pattern of growth with predominantly spindle cell growth in other areas (see Fig 2) (hematoxylin-eosin, original magnification ×100).

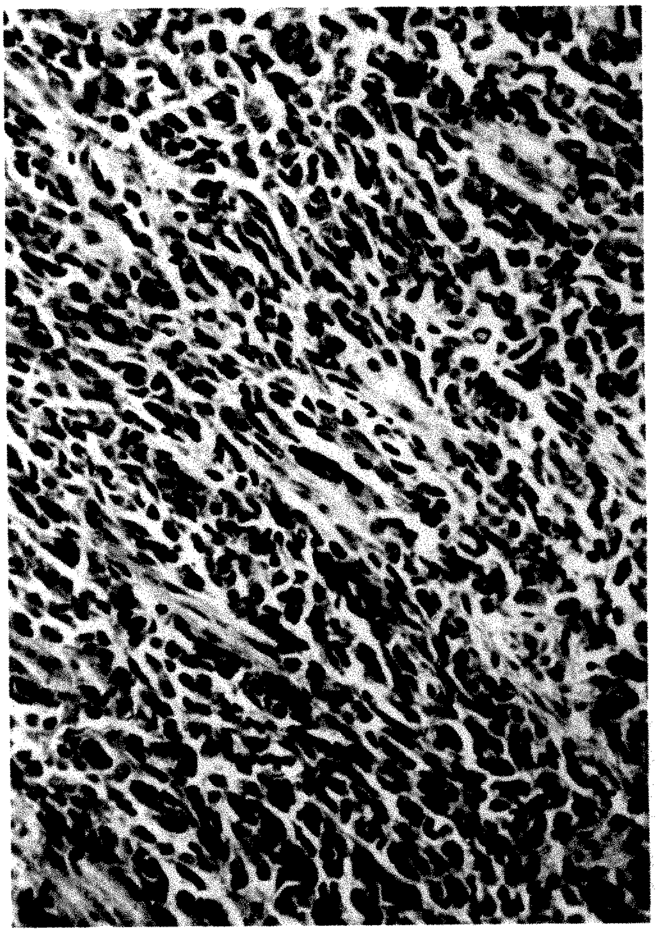

Fig 2.—Spindle cell area of growth of peritoneal mesothelium with mixed pattern of growth (hematoxylin-eosin, original magnification ×125).

tum as well as sheetlike peritoneal masses with some localized irregularities. Early detection of ascites by ultrasonography may allow earlier delineation of the tumor.[72]

Cytological examination of peritoneal fluid may yield the diagnosis of this tumor and may even classify the tumor,[7,8] especially if both light microscopy and electron microscopy are employed.[8,73,74] However, a high false-positive and false-negative rate has also been reported using this method.[75-77] Since normal mesothelial cells are commonly present in long-standing effusions, it may be difficult to establish whether they are benign or malignant on cytologic examination alone. When malignant cells are unequivocally present, an adenocarcinoma must be considered as the most likely primary cell type. Immunocytochemistry and electron microscopy may be of help in establishing the diagnosis unequivocally. Needle biopsy may yield the diagnosis of this tumor, although a greater quantity of tissue is preferred by pathologists for the establishment of the diagnosis.[7,8]

The surgical techniques available for definitive diagnosis of peritoneal mesothelioma include laparoscopy and laparotomy. Laparoscopy was first reported as a diagnostic tool in 1974.[28] It has been suggested as having a place in the early diagnosis of the disease if the index of suspicion is high.[9,30] Laparoscopic findings reveal innumerable nodules that stud the parietal peritoneum and their abdominal structures. The parietal peritoneal surfaces, rather than being inflamed, are densely coated with tumor nodules and plaques. In some cases, adherent bowel loops and adhesions are present.[78] Most diagnoses are either made or confirmed at laparotomy.

Laboratory studies may suggest the diagnosis. Malignant mesothelioma cells can produce hyaluronic acid; although this chemical may also be produced by other cell types, exclusion of intracellular mucin with a periodic acid–Schiff stain usually rules out carcinomas.[6,7] Both histochemical and biochemical quantification of high levels of hyaluronic acid in effusions are highly suggestive of the disease.[6] In immunopathologic studies, malignant cell populations have been positively identified by antimesothelial cell sera raised from cells cultured in serous effusions.[79] A new marker consisting of an antibody raised against a protein isolated from the cytoplasm of mesothelioma cells and used in immunofluorescence and immunoperoxidase procedures has consistently identified both benign and malignant mesothelioma cells histologically and cytologically. However, this marker has not been widely tested nor is it readily available for routine use.[80] These techniques promise to prove useful for the future establishment of an antemortem diagnosis.

A multidisciplinary approach to the treatment of peritoneal mesothelioma combines surgery, chemotherapy, and radiation therapy. The role of surgery is often limited by the advanced stage of the disease, which precludes any curative resection. Thus, operation in most instances includes only establishing a tissue diagnosis and performing palliative procedures as indicated. Examples of these procedures include bypassing obstructing lesions or debulking of the tumor.*

Multiple chemotherapeutic regimens have been reported, each having met with various degrees of success. There are a few reports of long-term survivors.[16,21,81,82] The following is a list of the various agents and combinations of agents that have been used:

1. dactinomycin, vincristine sulfate, cyclophosphamide sodium[13]
2. doxorubicin hydrochloride, cyclophosphamide, vincristine[20]
3. cyclophosphamide, vincristine, methotrexate sodium, and 5-fluorouracil sodium hydroxide[83]
4. doxorubicin, dimethyl-triazenoimidazole carboximide[27,84]
5. cyclophosphamide, vincristine[84]
6. bleomycin sulfate, vinblastine sulfate[84]
7. fluorouracil, methyl 1-(2-chlorethyl)3-cyclohexyl-1-nitrosourea (CCNU)[84]
8. mitomycin C[84]
9. hydroxyurea[84]
10. cisplatin[84]
11. dactinomycin[84]
12. fluorouracil with thymidine rescue[84]
13. doxorubicin, cisplatin[85]

The consensus is that chemotherapy appears to be moderately effective in the treatment of mesotheliomas[81-84] and that doxorubicin alone or in combination with other antineoplastic agents achieves the best response.[81,83] It is interesting to note that all of the chemotherapeutic combinations of single agents have been used for both peritoneal and pleural mesotheliomas. Intracavitary instillation of ^{32}P (radioactive phosphorus),[19,20,26,86] gold,[19] or cytarabine[87] has also been reported, again with limited success and an occasional account of a long-term survivor.

Radiation therapy usually has been used in combination with intracavitary instillation of various agents[85] or in combination with chemotherapy.[13,25,80-84,86] An increasing number of articles report combining both modalities with the hopes of achieving a better success.

The peritoneal variety of malignant mesothelioma follows a more virulent course than those of pleural origin with progressive gastrointestinal tract obstruction and debility. Death usually occurs within 1 year after the diagnosis.[8] Regrettably, there has been little change in the poor prognosis and the low median survival rate originally reported by Moertel.[8]

Occasional exceptions to the rule have been reported. Rogoff et al[86] described two patients treated with radiation therapy and intracavitary instillation of ^{32}P who survived more than 10 years. Karakousis et al[81] reported a case of complete clinical regression of a peritoneal mesothelioma for 3 years, and Brenner et al[82] reported a 17-year survival in a patient treated with radiation therapy, intracavitary ^{32}P, and cyclophosphamide.[82] This patient is the longest survivor in the literature.

The prognosis for peritoneal mesotheliomas in children appears to be the same as that in adults. Of the 41 cases recorded in the literature, 40 died of the disease within 2 weeks to 21 months.[20] Exceptions include the report of Kaufman and Stout[14] of a child who survived 6 years after operation.

COMMENT

Primary peritoneal mesotheliomas are very rare. In the majority of the pleural cases reported in the literature, a causal link can usually be established to asbestos exposure in the patient's working or living environment. In our series, this link could only be established for one of the seven patients reported. No asbestos exposure could be documented for the other six cases.

The clinical presentation of all of the cases in this series was fairly nonspecific. Their delay in diagnosis after a short symptomatic period, diagnostic workup, and surgical and chemotherapeutic management are not at variance with the reports in the literature. We do report an unusual case with a coexistent malignancy—transitional cell carcinoma of the bladder.

We report long-term survivors of 7 and 15 years. The 7-year survivor received chemotherapy and had his ascites controlled with a peritoneal-jugular venous shunt that was functional until his death, thus suggesting that this method can be used successfully in the management of malignant ascites from malignant peritoneal mesotheliomas. The 15-year survivor is still alive at the time of this writing. She has not received chemotherapy and is currently being followed up closely. No unusual factors leading to the long-term survival of this patient could be identified.

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Aortic Occlusion and Vascular Isolation Allowing Avascular Hepatic Resection

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• Occlusion of the supraceliac abdominal aorta and hepatic vascular isolation were employed in a series of 15 patients as a definitive method to allow avascular hepatic resection. The series was compared with an earlier group of patients treated conventionally. In the avascular hepatic resection group there was no mortality; hypotension did not occur at the time of hepatic vascular isolation; rapid, accurate excision of the hepatic lesions could be achieved in a bloodless field; resection of midline lesions and those involving the great veins was possible; and "segmentectomies," or resections crossing segmental boundaries, could be performed where previously formal hepatic lobectomies were required. Concomitantly, the greatest amount of uninvolved hepatic parenchyma remained in situ. There was increased ease of operative management, reduced blood loss, and reduced operating time (mean, 2.8 hours).

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Despite the development of refined surgical techniques based on the segmental anatomy of the liver,[1] blood loss remains a significant threat during hepatic resection. As a means to reduce blood loss, several surgical groups[2-8] have used a technique prior to resection that isolates the liver from the circulation by occlusion of the inferior vena cava (IVC) above and below the liver and of the hepatic artery and portal vein in the liver hilus. Hepatic vascular isolation (HVI) was researched originally by Heaney et al[2] in a canine model. They included occlusion of the abdominal aorta as a part of their procedure and described three clinical cases. Since then, others using HVI for hepatic resection have either avoided aortic occlusion entirely[3,4]; employed it infrequently, usually only in urgent or special circumstances[5,6,8]; or studied HVI with and without its application.[7] We could find no report of a series of patients requiring liver resection in which aortic occlusion was combined with HVI as a definitive procedure in all patients prior to hepatic resection. Herein, we describe such a series involving 15 patients. To evaluate the method, we compared the features of the operations and outcomes in these patients with those of 10 patients treated in the period before this series began by conventional hepatic resection.

PATIENTS AND METHODS

The patients in the avascular hepatic resection group (AHRG) were consecutive patients who underwent operation for presumed or proved hepatic malignancy after formal assessment between February 1988 and July 1989. The patients in the conventional group (CG) were also consecutive patients selected for hepatic resection between June 1985 and December 1987. No patients in either group had established cirrhosis.

In both groups, preoperative assessment included complete blood cell count, coagulation tests, liver function tests, and a full serum biochemical profile. Abdominal computed tomographic scanning and selective celiac and mesenteric arteriography with late-phase portal venography were performed in all patients. Some patients were investigated by IVC phlebography. All patients with malignant lesions had bone scans performed.

In the AHRG, patients with lesions confined to the liver were accepted for liver resection when it was thought that the lesions could be removed without compromising irretrievably the blood vessels of supply and drainage or the biliary system of the liver remnant. In the CG, patients were selected for resection when the lesions could be removed by hemihepatectomy or, in one case, by anatomical "segmentectomy."

In both groups, the abdomen was explored through a bilateral subcostal incision with a median vertical incision extending over the xiphisternum. In the AHRG, the liver was mobilized by dividing the falciform, right triangular, coronary, and left triangular ligaments, and the gastrohepatic omentum. The infrahepatic IVC was encircled above the renal veins below the right adrenal vein. The supraceliac abdominal aorta was approached through the crura of the diaphragm. Vascular clamps were applied to the aorta and infrahepatic IVC, and a soft-bowel clamp was applied to the portal triad in the free edge of the lesser omentum. The suprahepatic IVC was occluded with a vascular clamp. Hepatic resection was then undertaken with a scalpel, the lines of excision being at least 2 cm clear of the lesions whenever possible. If significant hypertension (systolic blood pressure $\geq$180 mm Hg) developed during the period of aortic clamping and hepatic resection, it was corrected by brief and partial release of the aortic clamp followed by its reapplication. After removal of the resected specimen, the transected blood vessels and bile ducts on the cut surfaces of the liver were oversewn or repaired with vascular sutures. The infrahepatic IVC clamp was released briefly and intermittently, and bleeding sites on the cut surfaces were secured. The infrahepatic IVC, suprahepatic IVC, and portal triad clamps were

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Table 1.—Types of Lesions Resulting in Hepatic Resection

Hepatic Lesions Requiring Resection	No. of Patients: Avascular Hepatic Resection Group	No. of Patients: Conventional Group
Metastatic malignancy		
Primary site		
Colon	6	1
Stomach	1	0
Cholangiocarcinoma	3	3
Hepatocellular carcinoma	1	2
Other malignant tumors		
Sarcoma	2	1
Squamous cell carcinoma	1	0
Carcinoid	0	1
Benign lesions		
Multiple adenomas	0	1
Caroli's disease	0	1
Focal nodular hyperplasia	1	0
Total	**15**	**10**

Table 2.—Details of Operations

Variable	Avascular Hepatic Resection Group	Conventional Group
Type of operation, No. of patients		
Hemihepatectomy	5	9
Hemihepatectomy with segment IV (part)	1	0
Segmentectomy	9	1
Segments VII, VIII	4	0
II, III, VIII	1	0
VIII, IV (part)	1	0
V, VI, IV (part)	2	0
VII, VIII, IV (part)	1	0
Aortic clamp time, min	6-38 (mean ± SD, 19.5 ± 7)	. . .
Blood loss, mean ± SD mL*		
All operations	1720 ± 800	3940 ± 1600
Hemihepatectomies	1650 ± 773	3920 ± 1597
Duration of operations, Mean ± SD†	2 h 50 min ± 35 min	3 h 55 min ± 35 min
Time in hospital following operations, d	17.9 ± 6.1	20.1 ± 11.1
Time since operation, mo	9 ± 6	36 ± 11

*$P<.05$.
†$P<.001$.

removed. The aortic clamp was then gradually released, the rate of release being determined by the degree of hypotension that occurred at this time. Bolus administration of 100- to 200-mL quantities of intravenous fluids was also employed to prevent or control hypotension. After final arterial release, the cut hepatic surfaces were again inspected for bleeding points, which were secured.

Patients in the CG had hepatic resection performed after formal hilar dissection with appropriate arterial, venous, and biliary ligation.

During the operations, arterial blood pressure was monitored continuously by means of an arterial cannula, as was central venous pressure via a venous cannula. All patients in the CG had Swan-Ganz catheters placed for continuous monitoring of pulmonary wedged venous pressure. In the AHRG, only the first four patients had Swan-Ganz catheters placed. Blood samples taken before and after hepatic resections were analyzed for pH levels, blood gas partial pressures, and coagulation and biochemical factors.

RESULTS

In the AHRG, there were 5 men and 10 women aged 25 to 68 years (mean ± SD, 58.4 ± 11.6 years). In the CG, there were 6 men and 4 women aged 35 to 63 years (mean, 55.4 ± 9.8 years). The types of lesions causing the need for hepatic resection in both groups are shown in Table 1. It can be seen that 14 of 15 patients in the AHRG had malignant lesions as did 8 of 10 patients in the CG.

Details concerning the type of operation including the portions of the liver removed in the segmentectomies are shown in Table 2. The segments referred to are according to the classification of Couinaud.[9] While one (10%) patient in the CG was treated by segmentectomy, nine (60%) patients in the AHRG were so treated. In the AHRG, five tumors involved segment IV. In none of these was a classic trisegmentectomy[1] performed. In all patients, either the upper or lower half of segment IV remained in situ after resection of the lesions contained within other segments and a portion of segment IV. In one of these patients, the cancer involved the IVC and the right and left hepatic veins. After removal of the lesion contained in the right segments and upper part of segment IV, both the IVC and left hepatic vein required reconstruction. The IVC was also involved in a solely right-sided malignancy, and again part of the IVC wall was removed with the lesion and the IVC defect repaired. There were three patients with hilar tumors in the AHRG and one in the CG. In all patients, the cancers involved the lobar portal veins and bile ducts. After appropriate hepatectomy, all patients required repair of two or three second-order bile ducts following division of branches of the left or right hepatic bile ducts. In two cases, it proved impossible to ensure a 2-cm clearance of the lesions during resection, once with a tumor subsequently recognized as a secondary liposarcoma that had an intrathoracic extension, and once when it became apparent that a primary hemangiosarcomatous lesion was multifocal in nature and complete clearance could not be achieved.

Other details of the operations are also shown in Table 2. In the AHRG, the time required for hepatic resection and hemostasis was the same as the aortic clamp time (mean ± SD, 19.5 ± 7 minutes). Blood loss was significantly less in the AHRG ($P<.05$) both for all operations and when only those patients treated by hemihepatectomy were considered. The mean duration of operations in the AHRG was 2 hours 50 minutes, which was significantly less than in the CG ($P<.001$).

All patients in the AHRG developed hypertension following application of the aortic clamp. In 12 patients, this was mild and required no intervention, but in 3, when systolic blood pressures in excess of 180 mm Hg persisted, control was easily achieved by monitored partial release and reapplication of the aortic clamp. Similarly, all patients in the AHRG showed a tendency to develop hypotension at the time of unclamping the aorta, but this was controlled by gradual release of the aortic clamp and bolus intravenous fluid administration.

Results from liver function tests performed before and after the operation are shown in Table 3. The mean preoperative test results were largely comparable between the groups, although the serum γ-glutamyl transferase, serum alanine leucine transferase, and serum bilirubin levels were all slightly higher in the AHRG. On the first day after operation, the serum albumin, serum alkaline phosphatase, and serum glutamyl transferase levels had all fallen in both groups but without significant difference between the two groups. The serum bilirubin level increased in both groups, the in-

Table 3.—Liver and Renal Function Test Results*

Test	Preoperative		Postoperative Day 1		Postoperative Day 3	
	AHRG	CG	AHRG	CG	AHRG	CG
Prothrombin index, %	99 ± 1	94 ± 3	39 ± 2	79 ± 3	96 ± 1	93 ± 3
Serum albumin, g/L	39.5 ± 1.5	41.5 ± 2	30.5 ± 1	34 ± 1.5	31 ± 1	33.5 ± 1.5
Serum alkaline phosphatase, U/L	158 ± 30	153 ± 35	97 ± 13	84 ± 11	126 ± 16	132 ± 34
Serum γ-glutamyl transferase, U/L	122 ± 47	86 ± 25	64 ± 19	36 ± 7	68 ± 15	45 ± 6
Serum alanine leucine transferase, U/L	85 ± 30	63 ± 30	404 ± 92	284 ± 73	328 ± 92	151 ± 35
Serum bilirubin, μmol/L	31 ± 12	12 ± 2.5	49 ± 10	65 ± 1	41 ± 10	40 ± 7
Serum creatinine, μmol/L	75 ± 7	84 ± 7	70 ± 8	77 ± 6	68 ± 7	72 ± 8

*Data are expressed as the mean ± SEM. AHRG indicates avascular hepatic resection group; CG, conventional group.

Table 4.—Operative Mortality and Complications

Variable	No. of Patients	
	Avascular Hepatic Resection Group	Conventional Group
Death	0	1
Primary hemorrhage	1	1
Fluid collections requiring		
Operation	1	0
Percutaneous drainage	3	3
Biliary fistula	0	1
Deep venous thrombosis	1	0
Malignancy		
Late deaths	1	2
Alive with known disease	2	3

crease being more substantial in the CG. All test levels were either stable or returning to normal by the third postoperative day. Regarding renal function, the preoperative and postoperative serum creatinine levels are shown in Table 3. No patient had renal failure at the time of operation, and there was no significant change in renal function in either group following operation. There were no significant variations in acid-base balance or in the coagulation or biochemical studies performed before and after hepatic resection in any patient in either group.

Operative mortality and complications are shown in Table 4. The only death that occurred was in the CG, where one patient died of hepatic failure following hemihepatectomy for a cholangiocarcinoma. The patients (one in each group) with primary hemorrhage required reoperation, as did one patient in the AHRG to evacuate a hematoma. The occurrence of malignancy in survivors recorded in Table 4 is documented for completeness and is not meant to be comparative, as the mean time since operation in the AHRG is 9 months, whereas the CG it is 36 months.

COMMENT

Use of the method described herein to allow avascular hepatic resection (AHR) was a direct extension of the standard methods for HVI, which are used during recipient hepatectomy prior to liver transplantation. To these was added aortic occlusion. Thus, our technique was virtually identical to that described by Heaney et al,[2] although we found it convenient to encircle the suprahepatic IVC below the diaphragm in all cases rather than within the pericardium as suggested by Heaney et al for adult patients. Inferior vena cava occlusion below the diaphragm has the benefit of exclusion of the diaphragmatic veins from the isolated part of the IVC either because the upper clamp is below their point of entry or because they are included in the upper clamp. The only tributaries of the isolated segment of the IVC that remain uncontrolled with this method are the right adrenal vein and variable lumbar veins. Flow through these veins must be greatly reduced because of the supraceliac aortic clamp, as the parenchymal resections following vascular isolation were virtually free of blood loss. We believe that the avascular nature of the resections accounted for the significantly reduced blood loss in the AHRG compared with the CG and allowed rapid hepatic resection and suture of divided blood vessels and bile ducts, which contributed to a significantly decreased overall operation time.

We consider that occlusion of the aorta during the period of hepatic resection and hemostasis is a critical factor in the success of applying HVI to liver resections. Without it, there is engorgement of the intestines and lower half of the body during the period of portal and caval interruption and this, together with reduction of venous return to the heart, predisposes to hypotension. Because of this, other studies[3-5,7] using HVI without aortic occlusion have emphasized the need for blood volume expansion and careful monitoring during the period of vascular isolation to control hypotension. Indeed, Bismuth et al[6] and Delva et al[7] advise trial clamping of the IVC and portal triad before proceeding to resection; if this results in severe hypotension, Bismuth et al recommend that resection with HVI should not be undertaken, while Delva et al use this as an indication for the addition of aortic occlusion to HVI. Furthermore, HVI without aortic occlusion is only partially successful in controlling hemorrhage, as moderate blood loss often continues during hepatic resections[3,6] because of retrograde flow into the liver from the uncontrolled tributaries of the isolated IVC. This appears to result in a somewhat prolonged vascular isolation and resection interval and to contribute to the overall length of the procedure. For example, Bismuth et al reported that the mean ± SD vascular isolation interval, blood transfusion requirement, and operating time were 46.5 ± 5 minutes, 4.5 ± 1.0 U of blood, and 5.8 ± 0.8 hours, respectively. The comparative figures in this report for the AHRG are 19.5 ± 7 minutes, 3.44 ± 1.6 U of blood, and 2.8 ± 0.6 hours, respectively.

Our conviction of the importance of aortic occlusion in association with HVI for hepatic resection appears to be at variance with the view of Delva et al[7] who believe that aortic occlusion is not necessary for this purpose. Delva et al described the hemodynamic and biochemical changes that occurred during major liver resection for massive liver tumors with HVI—with and without aortic occlusion. Their conclusion was reached on the grounds of good hemodynamic tolerance of HVI without aortic occlusion if accurate fluid volume loading had been achieved before HVI. However, they demonstrated that the hemodynamic and biochemical changes during hepatic resection were somewhat less in the presence of aortic clamping, as was the requirement for blood transfusion (mean, 2250 mL vs 5050 mL). Delva et al apparently considered that these benefits were outweighed by an incidence of unexplained transient ventricular arrhythmias in the aortic occlusion group together with the difficulty of aortic exposure if the left lobe of the liver is enlarged. We saw none of the former complications, and the latter difficulty may have reflected the massive nature of the liver tumors in their patients, as we were always able to use the standard expeditious approach to the supraceliac abdominal aorta via the diaphragmatic crura so that a vascular clamp could be applied without formal dissection. We concede that aortic occlusion is not necessary for resection with HVI, as has been demonstrated by all the groups using HVI; however, we believe that the improved hemodynamic and biochemical variables defined by Delva et al, together with the substantial practical benefits and absence of adverse effects detailed herein, comprehensively justify the requirement of aortic exposure and control as a part of the AHR method.

Potential disadvantages of adding aortic occlusion to HVI include any consequences of the hypertension that occurs at the time of aortic occlusion, of hypotension or acidemia at the time of release of the aortic clamp, and of ischemic damage to the organs and tissues below the level of the diaphragm during the period of aortic, portal, and IVC interruption. The potential disadvantages, however, did not eventuate. Mild hypertension developed during the resectional interval in all patients but required treatment in only 20%, which was readily achieved by brief release and reapplication of the aortic clamp. Because of absence of hypotension during HVI, blood volume expansion was not necessary. The trend toward development of hypotension at the time of release of the aortic clamp following resection was easily counteracted by gradual aortic release and bolus intravenous fluid administration. As might be expected because of the relatively short aortic occlusion times, there were no changes that could be related to increased ischemia of tissues and organs below the diaphragm. Acid-base disturbances did not occur. Liver function tests were no more disturbed in the AHRG than in the CG, and the modest abnormalities in the AHRG returned rapidly to normal following operation. There was no deterioration of results from renal function tests. There were no gastrointestinal or spinal cord complications.

A further potential disadvantage of this procedure may be an increased likelihood of recurrence of malignant disease following the more limited resections of the AHRG compared with the hemihepatectomies of the CG. However, we hope that the reverse will be true because of the greater certainty of clearance of malignant tissue ensured by resection under clear vision in the avascular livers, with the ability to remove involved areas of the IVC, hepatic veins, portal veins, or bile ducts. Indeed, our experience of recurrence following resection of malignant neoplasms by hemihepatectomy has been disappointing and is reflected in the CG, where malignancy is known to be present in 5 (71%) of 7 patients who survived operation for malignant lesions. In all 5 patients, evidence of malignancy was found within months of operation. In the AHRG, malignant disease is known to be present in 3 (21%) of 14 patients who received treatment because of malignant hepatic lesions, including both patients with sarcomatous lesions where adequate clearance could not be achieved. However, it is emphasized that no conclusions can be made in this matter, as the time since operation in this group is a mean of 9 months compared with the mean of 36 months in the CG.

Since we adopted the AHR method, the operative treatment of patients undergoing liver resection has become progressively less demanding. As we became increasingly familiar with the method and impressed with its speed and safety, we were able to dispense with some of the refined monitoring methods that had been routine in our previous practice. In particular, Swan-Ganz catheters to monitor pulmonary wedged venous pressure are no longer placed and the specialist anesthetic team assembled for liver resection during the time of the conventional technique has been disbanded. We are also using the method with some regularity in patients with major liver injuries following trauma.

The success of the AHR method has led to a distinct change in the types of resections that we perform. Whereas with conventional methods we elected to perform hemihepatectomy for most lesions in the liver, after applying the AHR method more limited resections became possible in the majority of cases. Moreover, safe and speedy resections without precise regard for the anatomic hepatic segments were possible. Although nine procedures in the AHRG are listed in Table 2 as segmentectomies, on four occasions resections deliberately transgressed segmental boundaries when, after the resection of other segments, either the upper or lower portion of segment IV was left in situ. In the remaining five cases, although the intention was broadly for segmental resection, the segmental boundaries were likely to have been transgressed because no precise anatomic guidelines were followed; that is, our indications for transsegmental resections have broadened to the point where this is the preferred method of resection, the operations increasingly resembling a *lumpectomy* as the term is applied to breast resections. As a result of more circumscribed resections, the greatest amount of uninvolved hepatic parenchyma is left in situ, a consideration perhaps having relevance for patients with hepatic malignancy complicating cirrhosis.

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Management of Perineal Wounds Following Abdominoperineal Resection With Inferior Gluteal Flaps

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• Our experience treating perineal wounds secondary to abdominoperineal resection, either for inflammatory bowel disease or cancer, is presented. A total of 16 patients were treated either on a delayed basis or at the same time as the abdominoperineal resection. All wounds were closed using the inferior gluteal myocutaneous flap. Fifteen of 16 patients have achieved healing, eight of whom had no complications. Only minor revisions or local wound care were required in the remaining patients, with only one patient failing to heal. Our results compare favorably with previous reports of treatment of this difficult problem.

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Perineal wounds following abdominoperineal resection (APR) for cancer or inflammatory bowel disease may be a significant source of morbidity if healing is delayed. We report our experience with the management of these wounds using inferior gluteal musculocutaneous flaps.

A total of 16 patients have been treated either on a delayed basis or immediately following the proctectomy. Of the 16 perineal wounds, six were secondary to APR for Crohn's disease, two developed following APR for ulcerative colitis, and eight were secondary to procedures for carcinoma. Fifteen of the 16 patients have achieved a healed wound. One patient with the diagnosis of Crohn's disease has failed to achieve closure at any time following the surgical procedure. Two patients treated after tumor resections have subsequently had recurrent tumor, which presented in the area of the perineal wound with some degree of ulceration. Our results compare favorably with previously reported cases of muscle flap closure of perineal wounds and are certainly superior to the more traditional methods of treatment of this difficult problem.

A significant source of morbidity following APR is the chronic perineal wound. Wounds that remain unhealed 6 months following proctocolectomy have been termed *persistent perineal sinus.*[1] The incidence of persistent perineal sinus following proctocolectomy has been reported to range from 25% to 55%,[2-4] with a higher incidence usually reported in patients with inflammatory bowel disease. Various methods have been described to manage the pelvic space after proctectomy, but none has eliminated the problem of persistent perineal sinus.[5-7] The pathogenesis and method of treating the persistent perineal sinus have been adequately described by Silen and Glotzer.[8] The problem is fundamentally that of a noncollapsible dead space caused by the anatomy of the pelvis, and any problems in primary wound healing simply compound the problem. Various methods of treating established sinuses have been reported, including gracilis flaps,[9,10] gluteal flaps,[11,12] skin grafts,[13] medical therapy,[14] and prolonged local wound care. We report our experience with inferior gluteal myocutaneous flaps in the treatment of this difficult problem. Initially, these wounds were treated on a delayed basis after the failure of conventional wound care. Later in our experience, several wounds were closed at the time of proctectomy when wound healing problems were anticipated for various reasons. Satisfactory results have been achieved using both methods of closure.

PATIENTS AND METHODS

All patients were treated by the authors within the Emory University Affiliated Hospitals, Atlanta, Ga. The hospital and office charts were reviewed and serve as the basis of the presented data.

Sixteen patients with perineal wounds secondary to proctocolectomy underwent wound closure with inferior gluteal myocutaneous flaps. Fifteen patients underwent closure with a single myocutaneous unit, while one patient required bilateral flaps for closure. Thirteen of the patients were treated on a delayed basis after the failure of convential wound care techniques to achieve healing. Three patients underwent closure with a gluteal flap immediately following or within days of the proctocolectomy. One of these patients had undergone wide pelvic dissection for recurrent carcinoma of the rectum and another required wide skin excision for an anal carcinoma. The third patient underwent closure 12 days after proctectomy, at which time the perineal wound was packed open followed by several dressing changes in the operating room.

Patient 14 (Table) presented with a chronic perineal wound with a retained rectal segment. She was treated with proctectomy, débride-

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Clinical Experience

Patient No./ Age, y/Sex	Diagnosis*	Time to Heal, wk	Time With Wound, mo	Complications	Revisions
1/28/F	Crohn's disease	Primary	24	...	...
2/23/F	Crohn's disease	Failed	8	Wound dehiscence/persistent sinus	Two local procedues
3/54/F	Carcinoma (RT)	2	5	Small dehiscence	...
4/48/M	Carcinoma (RT)	Primary	5	...	...
5/27/F	Crohn's disease	Primary	6	Late recurrent/ultimately healed	One local procedure
6/26/F	Crohn's disease	12	8	Small dehiscence	One local procedure
7/58/M	Carcinoma	24	12 d	Small dehiscence	One local procedure
8/58/M	Carcinoma (RT)	4	Immediate flap	Small dehiscence	...
9/20/M	Ulcerative colitis	Primary	12	...	...
10/18/M	Crohn's disease	Primary	5	...	...
11/59/M	Carcinoma (RT)	6	36	Infection, massive venous thrombosis	...
12/43/M	Carcinoma	Primary	Immediate flap	...	...
13/52/F	Carcinoma (RT)	12	36	Infection	...
14/75/F	Carcinoma	Primary	1	...	Gracilis muscle flap
15/68/F	Crohns disease	2	30	Perineal hernia	...
16/33/F	Ulcerative colitis	Primary	60	...	...

*RT indicates radiation therapy.

ment, and immediate flap closure but is grouped with the patients with delayed closure because of her long-standing perineal wound problems. Only one patient in this group had undergone a previous attempt at surgical closure, which consisted of a failed split-thickness skin graft. The remaining patients had been treated with local wound care only. In the patients treated on a delayed basis, the mean time that the perineal wound was present was 18 months, with a range of 1 to 60 months.

Eight patients had undergone proctectomy for inflammatory bowel disease; six had Crohn's disease and two had ulcerative colitis. The great majority of these patients had severe perianal disease prior to the proctectomy. Although most had received steroid therapy at some time during their clinical course, no recent steroid use was identified prior to the gluteal flap closure. Eight patients had undergone proctectomy for carcinoma and five of the eight had received radiation therapy.

Early in the experience a standard gluteal flap was elevated using the full thickness of the inferior aspect of the gluteus maximus muscle. Later wounds were closed using a modification requiring only partial thickness of the gluteal muscle.[15] Operative details are outlined in Figs 1 through 4. When the procedure was performed immediately after the proctectomy, the wound was temporarily covered with sterile towels. The patient was then repositioned to the prone position prior to completing the flap dissection and closure.

RESULTS

Uncomplicated healing was achieved in eight (50%) of the 16 patients. Of these eight, one patient with Crohn's disease developed a very small asymptomatic fistula approximately 10 months following the initial uncomplicated healing. This fistula persisted for 9 months, but has recently completely healed without any specific therapy. A second patient in this group later developed recurrent tumor that presented in the suture line of the perineal closure. Seven patients achieved a closed wound in a mean of 9 weeks, with a range from 2 to 24 weeks. Of the seven wounds with complicated healing, most problems were minor wound dehiscences or superficial infections. These problems were managed with dressing changes in three patients and minor débridement and flap reinsertion in three patients. The remaining patient required salvage with a gracilis muscle flap after the initial wound breakdown required further resection of the osteoradionecrotic pelvis. One patient with Crohn's disease has failed to achieve a healed wound in spite of several attempts at secondary débridement and flap reinsertion and now has evidence of extraintestinal Crohn's disease as well. Other complications have included massive ileofemoral venous thrombosis in one patient, probably secondary to recurrent tumor, and a recalcitrant perineal hernia in another patient. The results are presented in the Table.

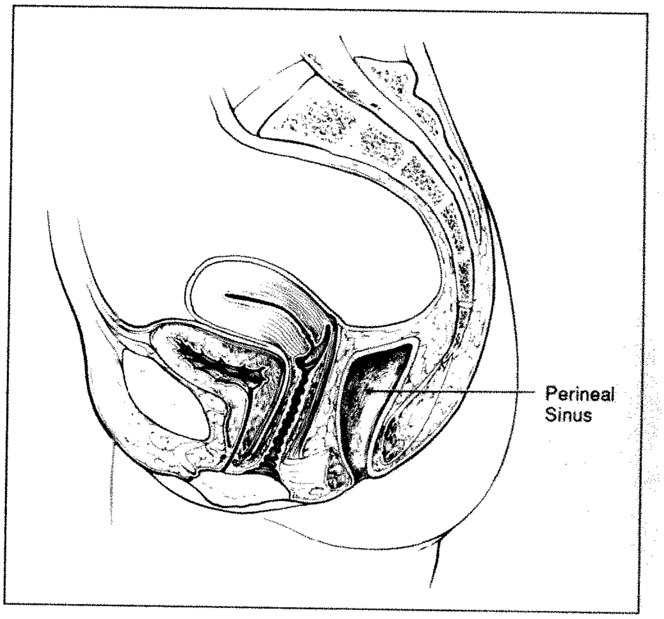

Fig 1.—The perineal sinus after proctocolectomy. The posterior surface of the sacrum and the chronic fibrous tissue lining are essentially noncollapsible walls that restrict spontaneous closure.

COMMENT

Abdominoperineal resection for carcinoma of the rectum was described by Miles[16] in 1908. The procedure was subsequently extended to the treatment of inflammatory bowel disease. A significant source of morbidity from the procedure has been and remains to be problems with the perineal wound. Persistent perineal sinus has been arbitrarily defined as a wound persisting beyond 6 months after APR. An interesting article by Knavel[17] describes techniques for treating similar

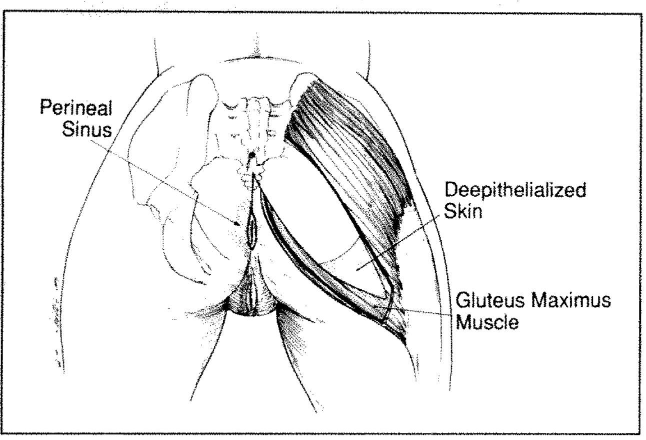

Fig 2.—The gluteus maximus musculocutaneous flap is designed over the lower third of the gluteus maximus muscle. The skin island may be designed either as an island or as a penisula-type flap.

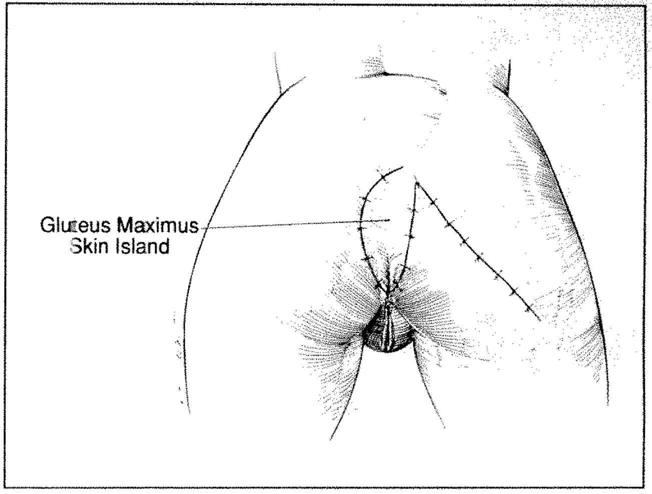

Fig 4.—Wound closure results in a donor scar of the buttocks. Closure of the skin posterior to the perineal defect can be done with a z plasty to reduce linear tightness. The skin paddle is a patch that fills the perineal defect.

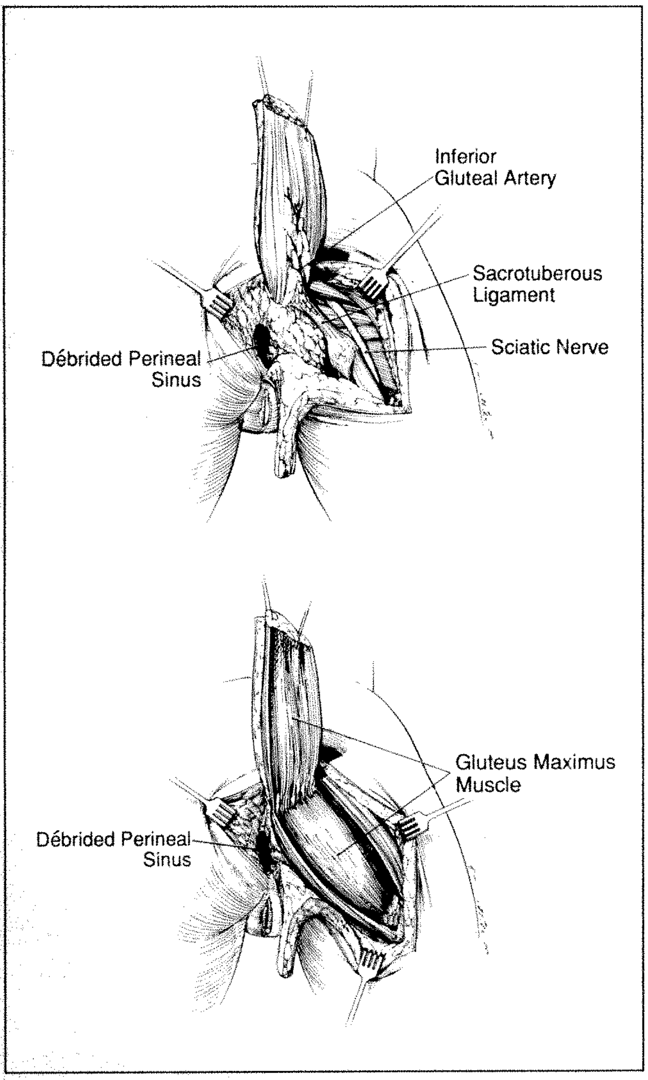

Fig 3.—Top, The gluteus maximus musculocutaneous flap (standard flap) is then elevated based on the inferior gluteal artery pedicle. It is then transposed into the pelvic and perineal defect. Bottom, The modified flap using a split-muscle technique. The deep remaining muscle protects underlying structures while the superficial muscle provides adequate vascular supply to the overlying skin.

wounds as early as 1920. Unfortunately, the concept was lost until the rediscovery of muscle flaps in the early 1970s.

Silen and Glotzer[8] have discussed both uncomplicated perineal wound healing and the reasons for the development of a persistent perineal sinus. Uncomplicated healing of the perineal wound occurs because the pelvic cavity is obliterated, and various methods of perineal closure have been advocated to assist in this obliteration of the pelvic dead space. Due to the anatomy of the pelvis, the dead space remaining after proctocolectomy is essentially a noncollapsible space analogous to the pleural space after pneumonectomy. If perineal wound healing is delayed for any reason, inflammation in the area leads to an even more fibrotic and rigid wound. Thus, the persistent perineal sinus is similar to the chronic empyema cavity, which is unable to collapse and close by normal wound-healing mechanisms.

Recently, there have been various reports of closure of perineal wounds using muscle flaps, with the gracilis being the most widely used. Mathes et al[18] reported success in all five patients treated with gracilis transposition, with a mean follow-up of 2 years.[18] Pezim et al[10] reported healing in 66% of 21 patients treated with gracilis flaps, with 71% of these patients requiring further perineal operations to achieve healing in a mean period of 2 to 3 months. Of note, skin slough occurred in 50% of the musculocutaneous flaps using the gracilis unit. Woods and Beart[19] reported healing in 13 of 14 perineal wounds treated with gracilis muscle flaps. Twelve of these 14 wounds were secondary to proctocolectomy. The exact details of healing time are not clear, however; other procedures were required in at least five patients and one patient has never achieved healing. Ryan[9] reported healing in 12 of 15 patients with persistent perineal sinus secondary to inflammatory bowel disease. Of the remaining patients, one failed completely to achieve healing and two achieved improvement. Of the healed wounds, only three healed primarily, with the remainder requiring either further surgery or several months of secondary healing. Baek et al[20] have reported comparable results.

All of these series using gracilis muscle or musculocutaneous flaps achieved superior results compared with more conventional methods of treatment; however, problems with prompt and eventual wound healing remain. We believe that the gluteus musculocutaneous flap offers two distinct advantages over the gracilis flap. First, the gluteus provides a large bulk in close proximity to the dead space to be obliterated; therefore, the wound is reliably obliterated using only one flap in almost all instances. Second, the skin island is much more reliable than that available using the gracilis.

Using the gluteus myocutaneous flap, we achieved uncomplicated healing in eight of 16 patients; this was achieved in both chronic wounds and in perineal wounds reconstructed immediately. In the remaining patients, seven wounds healed within a mean of 9 weeks following the initial procedure. Further surgical procedures to obtain healing consisted of minimal débridement and reinsertion of the original flap, except in one patient who required further débridement and gracilis salvage. This patient had a heavily radiated wound and extensive pelvic osteoradionecrosis. Only one patient failed to achieve wound healing at any time. We believe that the results of this technique are superior to those of using the gracilis muscle or musculoctaneous flap.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Long-term Irreversibility of Bone Loss After Surgery for Primary Hyperparathyroidism

Philippe Martin, MD; Pierre Bergmann, MD; Clémentine Gillet, MD; Michel Fuss, MD;
Jacques Corvilain, MD; Jean Van Geertruyden, MD

We reported previously that radial bone mineral content was decreased in patients with primary hyperparathyroidism and remained subnormal 1 year after surgery. In this study, we reviewed the results of sequential measurements of the radial bone mineral content, performed up to 107 months after removal of the parathyroid adenoma in 71 patients suffering from primary hyperparathyroidism. Bone mineral content increased during the first year after surgery. During the period 1 to 8 months after removal of the adenoma, the mean monthly increment was 0.009 ± 0.0022 g/cm for the radial epiphysis and 0.0084 ± 0.0023 g/cm for the shaft. However, in 39 patients seen at the end of 1 year after surgery, the bone mineral content of the epiphysis remained more than 1 SD below the normal mean in 61% (24) of the patients and more than 2 SDs in 36% (14) of the patients. For the shaft, those percentages were 59% (23) and 26% (10), respectively. Thereafter, the monthly increment rate of bone mineral content decreased rapidly with time, so that only minor further increase could be expected. Data show that patients with a low bone mineral content when diagnosed with primary hyperparathyroidism will conserve life long an irreversible loss of bone as compared with a matched control population (*Arch Intern Med*. 1990;150:1495-1497).

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Antibiotic Pharmacokinetics in Surgery

Donald E. Fry, MD, David E. Pitcher, MD

• Pharmacokinetics is the study of variables that affect drug concentrations at the effector site. The descriptive terms *peak concentration, elimination half-life, volume of distribution,* and *bioavailability* are commonly used to express pharmacokinetic variability among drugs used in patient care. The pharmacokinetic characteristics of drugs are important for surgeons to understand because they represent differences that may assume clinical significance when selecting antibiotics for preoperative preventive indications. In addition, the changing hemodynamic pattern of the stressed and septic patient may result in changing pharmacokinetic patterns for an antibiotic, which, in turn, may require changes in the dosing regimen during the course of treatment.

(*Arch Surg.* 1990;125:1490-1492)

The pharmacokinetics of antibiotics (and other drugs) is commonly discussed by pharmacologists in unfamiliar descriptive terms that are poorly understood by surgeons. Because surgeons use antibiotics in many areas of their practice, a greater awareness of pharmacokinetics and its clinical significance is important.

PHARMACOKINETIC PRINCIPLES

Pharmacokinetics is the study of variables that govern the concentration of a drug at its effector site. The drug is administered and absorbed into the central pool, or serum, of the patient. Oral drugs are absorbed over variable lengths of time, while intramuscularly administered antibiotics are absorbed more rapidly and with less variability than orally administered drugs. Both oral and intramuscular administration have a sustained-release profile, which means that drug metabolism or excretion will begin prior to complete absorption of a given dose. Thus, concentrations in the central pool are influenced by both rates of drug uptake from the gut or intramuscular reservoir, and the rates of drug metabolism or excretion. With intravenous administration, drug absorption is virtually immediate so that the central pool concentration becomes a consequence of drug elimination alone.

As the drug concentration in the central pool rises, gradients for diffusion into the various tissues occur. The equilibrium state between the central pool and any tissue is governed by multiple variables. The total blood supply, the lipid content of the tissue, the lipophilic or lipophobic character of the drug, and the protein-binding characteristics of the drug will each affect the rapidity of drug delivery at the tissue site. Thus, drug concentration will rise more quickly in well-vascularized muscle as opposed to relatively avascular fat tissue. If the drug is lipophilic, fat tissue concentrations will steadily rise as long as the central pool concentration exceeds the fat tissue concentration, but will then have sustained tissue concentrations even though serum concentrations will subsequently become negligible. Highly protein-bound drugs will diffuse less rapidly into the interstitial space than non–protein bound drugs, and will largely be excluded from intracellular water. The important point of this discussion is that serum concentrations may have no correlation with the concentrations at the target site.

Peak concentration (PC) of any drug in serum after intravenous administration is illustrated at point A in Fig 1. Peak concentration is the greatest concentration of drug in serum following a single dose. Peak concentration occurs very rapidly after intravenous administration, is somewhat delayed (12 to 15 minutes) after intramuscular administration, and may not occur until much later with oral administration. Point C in Fig 1 represents the equilibrated maximum concentration of the antibiotic. This reduced concentration when compared with point A occurs as a consequence of equilibration between the tissues and the central pool.

The time required for the drug serum concentration to decline by one half is then defined as the *elimination half-life* ($t_{1/2}$). When declining drug concentrations from metabolism or excretion are recorded on a semilogarithmic plot, the rate of drug elimination becomes linear and reflects the slope of the line. The $t_{1/2}$ remains constant over a broad range of concentrations, such that the duration of drug presence in serum can be described as multiples of that $t_{1/2}$. Thus, changes in the function or perfusion of organs responsible for drug elimination will have an impact on $t_{1/2}$ and the necessary dosing interval for the antibiotic being used.

Volume of distribution (VD) represents the theoretical volume of body water necessary to dissolve a given dose of a drug, assuming no elimination. This is calculated by extrapolation of the equilibrated elimination slope to point B, or time-zero concentration on the ordinate (Fig 1). Point B is the extrapolated concentration of the drug in serum after full equilibration among all tissues, but without any elimination.

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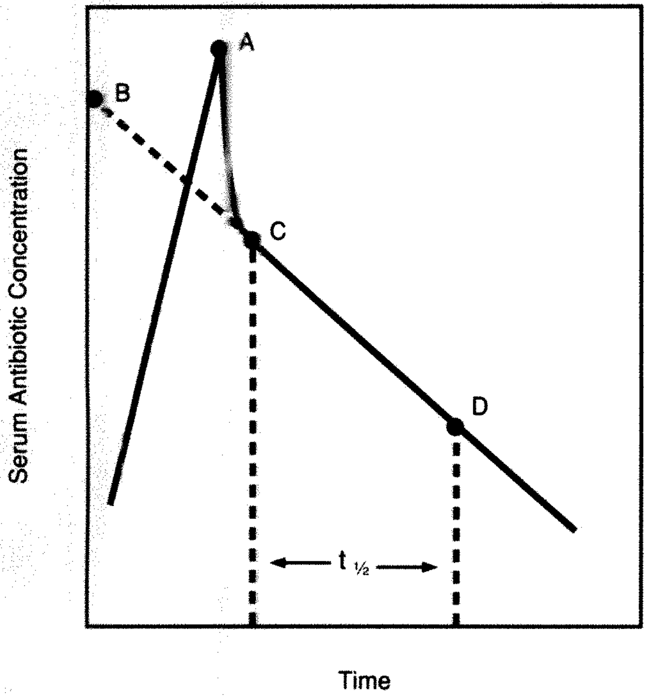

Fig 1.—The serum concentrations of a theoretical antibiotic given to a patient. Point A is the peak serum concentration; B, the extrapolated, time-zero concentration that is useful in the calculation of the volume of distribution; C, the maximum equilibrated serum concentration; and D, the concentration of the antibiotic in serum that is one half of point C and thus defines the elimination half-life ($t_{1/2}$) of the antibiotic. The area under the curve represents the bioavailability of the drug. The time interval from administration until the drug concentration dropped below the minimum acceptable therapeutic concentration represents the therapeutic availability. The plot is given a linear configuration because the drug concentrations are expressed as the logarithm of the actual values.

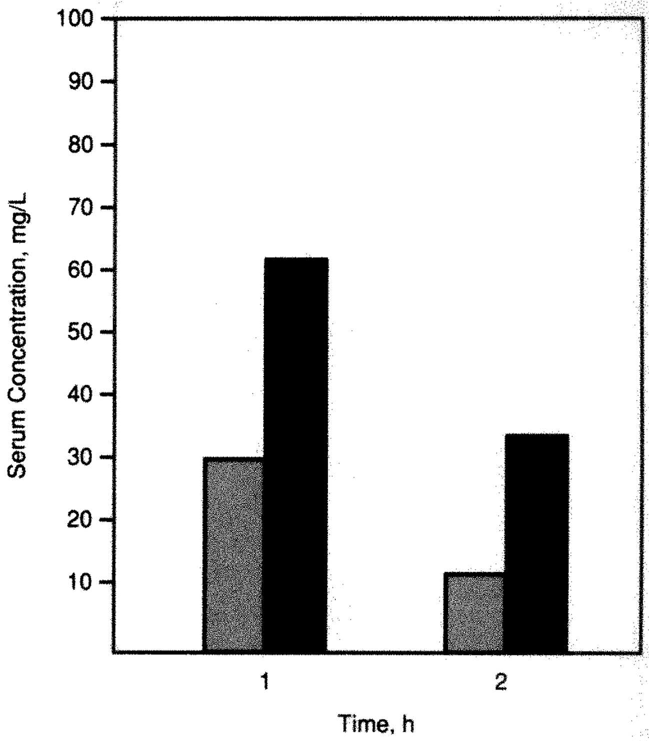

Fig 2.—The serum concentrations in milligrams per liter after preoperative administration of cephalothin (2 g given intravenously) and cefazolin (1 g given intravenously) in patients undergoing cholecystectomy. Shaded bars represent cephalothin; closed bars, cefazolin.

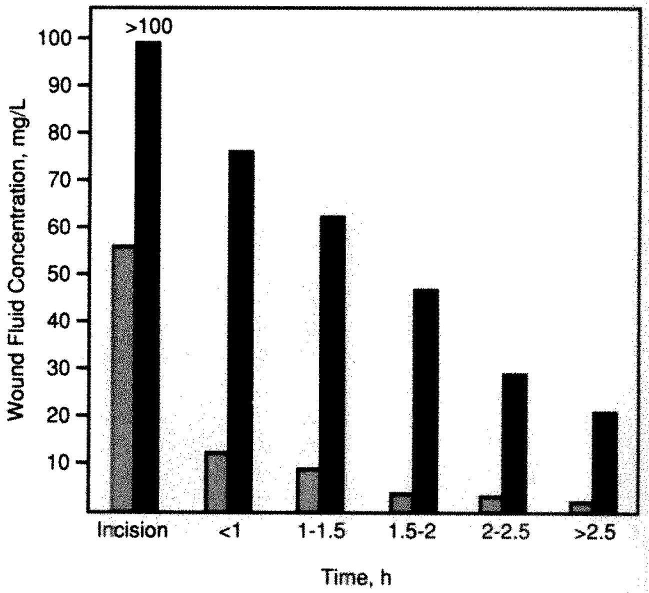

Fig 3.—The wound fluid concentrations in milligrams per liter after preoperative administration of cephalothin (2 g given intravenously) and cefazolin (1 g given intravenously) in patients undergoing cholecystectomy. Shaded bars represent cephalothin; closed bars, cefazolin.

Thus, a 1-g (1000-mg)-dose that results in an extrapolated time-zero concentration of 50 mg/L would have a VD equal to dose/time-zero concentration, or 1000 mg/(50 mg/L) = 20 L. Knowing that a patient weighing 70 kg has an extracellular water volume of 14 L means that this drug most likely penetrates the intracellular water volume to have a VD of 20 L. The determination of the VD assumes significance by virtue of dictating the maximum PC in serum for a drug with a given $t_{1/2}$.

Another common term used in pharmacokinetics is *bioavailability*. Bioavailability represents the area under the curve of the serum concentration plot. Drugs with high PC, small VD, and longer $t_{1/2}$ will have greater bioavailability than drugs with low PC, large VD, and short $t_{1/2}$. Differences in bioavailability explain why drugs with similar elimination $t_{1/2}$ may actually have different redosing intervals.

Therapeutic availability is our term, chosen because it is more clinically applicable. Therapeutic availability is the duration of time by which the antibiotic concentration exceeds the targeted therapeutic concentration that is desired for treatment objectives. Antibiotics with high PC but very short $t_{1/2}$ have a large calculated bioavailability but with a short redosing interval. The actual duration of antibiotic concentration or therapeutic availability that is greater than or equal to the minimum inhibitory concentration for the bacteria likely to be encountered is relatively short. Drugs with lower PC, but long $t_{1/2}$, may have a smaller bioavailability but a longer therapeutic availability by virtue of a longer period of time above the minimum inhibitory concentration. Because of differences in target tissue pharmacokinetics, an ideal design would be to know the therapeutic availability at the tissue site rather than in serum.

CLINICAL SIGNIFICANCE OF PHARMACOKINETICS

A first example that underscores the significance of pharmacokinetics can be seen in the use of antibiotics for preventive indications. Early studies in antibiotic prevention of infection for elective gastrointestinal resections demonstrated significant benefits from preoperative use of cephaloridine[1] or cefazolin sodium.[2] Subsequent studies using cephalothin sodium[3,4] showed no benefit, despite the similar antimicrobial spectrum of this cephalosporin compared with cephaloridine and cefazolin. However, measurement of serum (Fig 2) and tissue (Fig 3) concentrations of cefazolin and cephalothin demonstrated lower cephalothin concentrations at each time period.[5] Cefazolin has a greater PC, a lesser VD (it is highly protein bound), a $t_{1/2}$ of 2 hours, and a therapeutic availability of 4 hours. Cephalothin has a lesser PC, a greater VD, a $t_{1/2}$ of 35 to 40 minutes, and only a 75- to 90-minute therapeutic availability. The failure of cephalothin, and the success of cephaloridine and cefazolin, as preventive antibiotics emphasize the importance of therapeutic availability in covering the period of bacterial contamination.

An additional example can be identified in the use of aminoglycosides for therapeutic indications. Septic and stressed patients generally demonstrate a hyperdynamic circulation, which, in patients with normal kidney function, will result in accelerated excretion of the drug.[6,7] Pharmacokinetic dosing, while initially advocated to prevent toxic effects of aminoglycoside antibiotics, is now commonly used to ensure adequacy of drug administration. Up to five times the daily recommended dose of aminoglycosides may now be required in these patients with very elevated cardiac outputs. One can only speculate about the underdosing of other antibiotics or drugs that occur in the hyperdynamic setting.

In summary, drug pharmacokinetics has been ignored by surgeons. An understanding of pharmacokinetics is necessary if we are to optimize the clinical applications of antibiotics for the care of the surgical patient.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Compliance Declines Between Clinic Visits

Joyce A. Cramer; Richard D. Scheyer, MD; Richard H. Mattson, MD

Adherence to prescribed drug dosing regimens declined substantially during the interval between clinic visits and drug level tests. Using microelectronic monitors to observe pill-taking habits, 20 patients averaged 88% compliance before and 86% compliance after the visit, but this dropped to 67% compliance a month later. These data indicate that spot drug levels do not represent long-term "steady-state" drug serum concentrations (*Arch Intern Med.* 1990;150:1509-1510).

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This article is the continuation of a series of historical narratives to acquaint our readers with the contributions of surgeon-investigators to the investigation, development, and management of specific diseases and operations.

A History of the Bilioenteric Anastomosis

Steven A. Ahrendt, MD, Henry A. Pitt, MD

• The bilioenteric anastomosis has played an integral role in the surgical management of biliary tract disease during the past century. A wide variety of techniques for suturing a portion of the biliary tract to the digestive tract have been described since von Winiwarter's first cholecystoenterostomy. Many types of biliary stents have also been developed, although their exact role remains controversial. Many advances in preoperative and postoperative care have contributed to the low morbidity and mortality of current reconstructive biliary tract surgery.
(*Arch Surg.* 1990;125:1493-1500)

The introduction of general anesthesia and antisepsis laid the foundation for the tremendous advances in intra-abdominal surgery that occurred during the latter part of the 19th century. Surgery of the biliary tract was no exception. The standard therapies for gallstone sufferers, the Carlsbad cure or opiates, were largely unsatisfactory. Cholecystostomy, first performed by John Stough Bobbs in 1867, and cholecystectomy, initially peformed by Carl Langenbuch in 1882, rapidly assumed a prominent role in the management of gallstone disease.[1,2] Complications of these early surgical endeavors were frequent owing to the inexperience of the surgeons and often advanced inflammation at surgery. The resulting biliary fistulas or strictures necessitated the development of new means of rerouting bile into the digestive tract. In this setting, a wide variety of bilioenteric anastomoses were first described. The relief of symptoms with biliary decompression led to rapid application of bilioenteric anastomoses to malignant biliary obstructions.

THE ADVENT OF BILIARY SURGERY

Cholecystoenterostomy

Johann Nepomuk Ritter von Nussbaum of Munich, Germany, is credited with initially suggesting in 1870 that the construction of an anastomosis between the gallbladder and alimentary tract might successfully decompress a distally obstructed biliary tree.[3] However, the first attempt at cholecystoenterostomy was undertaken in 1880 in Liège, Belgium, by Alexander von Winiwarter (Fig 1).[4] A pupil of Theodor Billroth, von Winiwarter had recently assumed the professorship of Surgery in Liège in 1878.[3,5,6] By that time, he had distinguished himself by assisting Karl Gussenbauer in developing a gastrectomy technique in dogs, revising Billroth's text *Allgemeine Pathologie und Therapie*, and reporting one of the first series of surgical resection for breast cancer with long-term cures of the disease.[5-7]

In 1880, a 34-year-old man with signs of common bile duct obstruction and an enlarged gallbladder was referred to von Winiwarter. Attempts at aspiration of the gallbladder failed to relieve the symptoms and led von Winiwarter to explore the patient on July 20, 1880. He planned to create an internal biliary fistula. Finding the ascending colon adjacent to a markedly dilated gallbladder, he elected to suture the gallbladder to the colon instead of the jejunum, as previously planned. Both structures were exteriorized, and 4 days later a fenestrated trocar was passed through the gallbladder and into the colonic lumen, where the two structures had previously been joined. This procedure was unsuccessful, and when the trocar was removed 8 days later, the patient was left with a complete external biliary fistula.[3,4,8]

A second attempt at internal biliary drainage in the same patient involved the same technique, but with a larger trocar. It also failed and resulted in a second external fistula. The patient's condition continued to deteriorate, and on November 20, 1880, another attempt was made to close the fistulas. The cholecystocolostomy was taken down, and the contracted gallbladder was sutured to a loop of small intestine. Despite this new anastomosis, no reduction in external drainage occurred. In a fifth stage, von Winiwarter attempted to resect the fistulous tract and directly close the fistulous opening in the gallbladder with a skin flap. This procedure was also unsuccessful and left the patient with a persistent biliary fistula and two enteric fistulas where inadvertent enterotomies had occurred.[3,4,8]

At this point, the disenchanted patient disappeared from von Winiwarter's care and was not heard from until months later, when the referring physician notified von Winiwarter that the patient had markedly improved. Only a small amount of external drainage persisted, and the patient wondered whether anything further might be done to close the remaining fistulas. In a sixth stage 16 months after the initial procedure, a final attempt to close the enteric fistulas was undertaken. All drainage ceased in April 1892. Von Winiwarter

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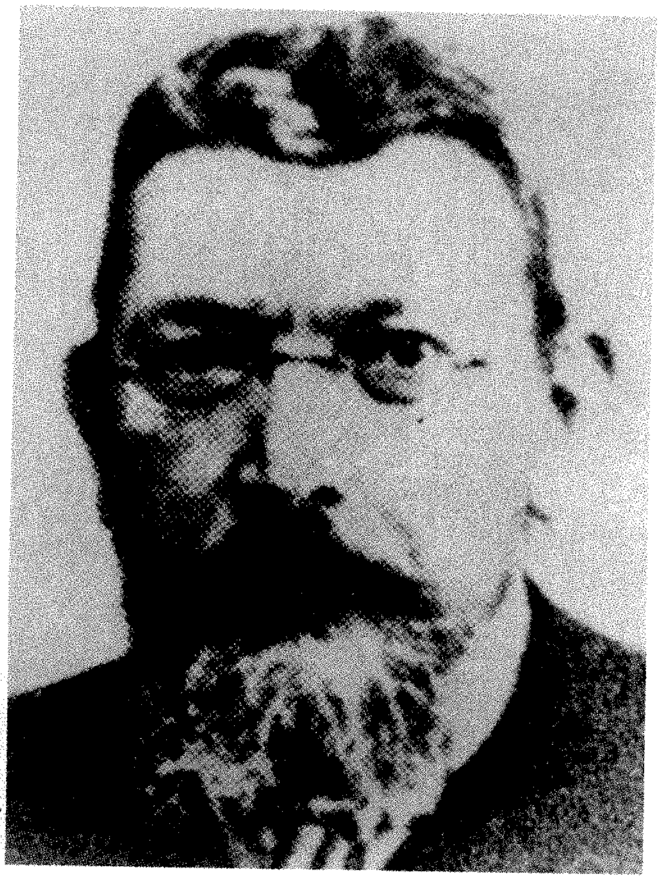

Fig 1.—Alexander von Winiwarter performed a cholecystocolostomy in 1880[4,6] (from Rutledge[6]).

concluded his initial case report by advocating a two-stage cholecystoenterostomy for cases of common bile duct obstruction.[3,4]

Von Winiwarter's experience dissuaded other attempts at cholecystoenterostomy for 5 years.[9] However, successful experimental studies in dogs by Colzi in Italy and J. M. Gaston in Atlanta, Ga, proved it to be a feasible procedure.[10,11] In 1883, Colzi described five dogs in whom he had performed cholecystoenterostomy after common bile duct ligation. All the animals survived without any apparent disturbance in digestive function.[9,11] Colzi also advocated cholecystoenterostomy vs cholecystocolostomy to minimize the possibility of ascending infection.[12] Gaston had less success, but did establish several cholecystoduodenal fistulas in dogs by using one full-thickness suture to join the gallbladder with the adjacent duodenum.[13] These encouraging results led to seven further cases of cholecystoenterostomy between 1887 and 1889.

In 1887, the Russian surgeon Monastyrski performed a one-stage cholecystojejunostomy in a 50-year-old patient with metastatic periampullary carcinoma and recurrent acute cholangitis (Table 1).[14] One month later, O. Kappeler successfully performed a similar operation in a patient with pancreatic cancer. Kappeler became the first to apply Anton Wolfler's technique of circumferential mucosa-to-mucosa intestinal suturing to the construction of a bilioenteric anastomosis.[8,9] Both patients were considerably improved by the procedure, but eventually succumbed to metastatic cancer. Autopsies of both patients confirmed anastomotic patency at death.

Use of the adjacent duodenum to establish continuity between the gallbladder and the alimentary tract was first attempted by Bardenheuer in two patients, one of whom died during surgery.[8] His technique involved elastic rubber bands that joined the gallbladder and duodenum and relied on pressure necrosis to establish a fistula. This method, however, was never proven to actually establish a patent cholecystoduodenostomy.[8] In 1889, the French surgeon Terrier performed the first successful cholecystoduodenostomy over a 4-cm rubber tube in a 54-year-old woman with an impacted common bile duct stone.[9,15] He was also the first to employ an internal stent in the construction of an anastomosis. The stent, however, passed 7 days after surgery.

Table 1.—Milestones in Early Biliary Surgery

Year	Investigator	Cholecystoenterostomy
1880	von Winiwarter[4]	Cholecystocolostomy
1887	Monastyrski[14]	Cholecystojejunostomy
1889	Terrier[15]	Cholecystoduodenostomy
1892	Gersuny[16]	Cholecystogastrostomy
		Choledochoduodenostomy*
1891	Sprengel[24]	Choledochoduodenostomy (S-S)
1898	Halsted[26]	Choledochoduodenostomy (E-S)
1902	Kehr[19]	Hepaticoduodenostomy (E-S)

*S-S indicates side-to-side; and E-S, end-to-side.

In 1888, A. W. Mayo Robson, Professor of Surgery at the University of Leeds, England, became the first to successfully treat a patient with an external biliary fistula through construction of a bilioenteric anastomosis. His patient had undergone cholecystostomy for empyema of the gallbladder and had drained a pint and a half of bile daily for 15 months. Adhesions obscured the duodenum, so Robson used the nearby hepatic flexure in construction of the anastomosis. His success led him to propose cholecystoenterostomy in the management of persistent biliary drainage following cholecystostomy.[8,10] However, an increased risk of cholangitis and the exclusion of bile from any role in digestion was recognized early and made the use of the colon unpopular in biliary reconstruction.

The stomach was initially used of necessity in reconstruction of the biliary tract. In 1892, another Billroth pupil, Robert Gersuny, explored a 45-year-old woman with episodic biliary colic and jaundice.[16] Dense adhesions encased the entire duodenum and small intestine, leaving only the stomach and colon available to bypass a potentially obstructed common bile duct. Despite Robson's previous success using the colon, Gersuny elected to suture the gallbladder to the prepyloric lesser curvature to preserve the normal function of bile in digestion.[8,16]

In his 1890 summary of the first 10 cholecystoenterostomies, Ludwig Courvoisier[9] concluded that cholecystoenterostomy could successfully compete with cholecystostomy and be performed with an acceptable mortality rate (20%). He advocated its use in cases of non–gallstone-related common bile duct obstruction and high-output biliary fistula after ductal injury or cholecystostomy, a frequent outcome after the most commonly performed biliary tract operation of that time. However, enthusiasm for the procedure was not initially widespread. Robert Lawson Tait,[17] one of the pioneers of abdominal surgery and a firm proponent of cholecystostomy, declared that cholecystoenterostomy was a fanciful operation not possible when most required—in cases of suppurative cholecystitis. Nevertheless, during the next several years, cholecystoenterostomy became popular as operations on the common bile duct were considered more formidable.[8] In an address to the 1894 International Congress of Surgery in Rome, Italy, John B. Murphy of Chicago, Ill, broadly advocated cholecystoenterostomy for all cases of common bile duct obstruction, cholecystitis, chronic discharging biliary fistulas, and perforation of the common bile duct.[18,19]

Choledochoenterostomy

Reconstruction of the biliary tract using the common bile duct became a necessity following the introduction of cholecystectomy for gallstone disease in 1882. Langenbuch suggested in 1884 that choledochotomy might be performed to remove common bile duct stones and that choledochoenterostomy could be performed on ectatic common bile ducts.[3,20] Choledochoduodenostomy was also suggested by the Swiss surgeon Theophil Roth[21] in 1885 for periampullary malignant neoplasms. Following a fatal attempt at choledochotomy by Hermann Kummell in 1884, successful choledochotomies were performed by Knowsley, Thornton, and Heusner in 1889 and by Courvoisier in 1890.[8,12,22,23]

In 1891, Oskar Sprengel[24] of Dresden, Germany, described the first attempt to establish an anastomosis between the common bile duct and the gastrointestinal tract (Table 1). After performing a cholecystectomy, he was unable to clear the distended common bile duct of stones. To prevent bile leakage from the cystic duct stump, he constructed a two-layer, side-to-side choledochoduodenostomy to decompress the distended common bile duct. After surgery, the patient had no evidence of biliary obstruction.[8,24] The German surgeon Bernhard Riedel had performed a similar procedure in 1888, but his patient died one day after surgery.[8]

Choledochoduodenostomy was performed less frequently after its initial description than cholecystoenterostomy because of its greater technical difficulty. Nevertheless, Robson and Dobson[18,25] advocated ductal anastomosis whenever clearance of gallstones from the common bile duct was impossible. They recognized that symptoms could persist if cholecystoenterostomy was performed. Choledochoduodenostomy was also used to reconstruct the biliary tract after resection of periampullary cancers. In 1898, William Steward Halsted resected a periampullary cancer and reconstructed the biliary tract with an end-to-side choledochoduodenostomy.[26] However, at reexploration 3 months later, the anastomosis was not patent, and a cholecystoduodenostomy was performed. Choledochoduodenostomy was finally established in 1913 as an operation with acceptable morbidity when Franz Sasse of Frankfurt, Germany, described 11 such successful operations. He recommended choledochoduodenostomy, when possible, as the procedure of choice. He believed that it prevented ascending cholangitis and gallstone formation associated with chronic common bile duct obstruction.[27,28]

Hepaticoenterostomy

Obliteration of the common bile duct through stricture or malignancy necessitated use of the more proximal common hepatic duct in establishing internal biliary drainage. In 1902, the German surgeon Hans Kehr resected a cancer at the junction of the cystic and common hepatic ducts. He performed the first hepaticoduodenostomy by reconstructing the biliary tree in an end-to-side fashion.[29] In 1905, William J. Mayo[30] described a patient with an obliterated common bile duct and an external biliary fistula following cholecystectomy and choledochotomy. Mayo's single-layer hepaticoduodenostomy was the first performed in the United States (Fig 2). Mayo described a semilunar duodenotomy designed to act as a partial valve to prevent ascending cholangitis.[30,31] Nineteen years later, the patient had no biliary tract problems and had survived pneumonia and typhoid fever.[32]

In the quarter century following von Winiwarter's cholecystoenterostomy, a wide variety of operations were introduced that firmly established the role of surgery in the management of biliary tract disease.[12] Murphy's series of 79 cholecystoduodenostomies with a 16% operative mortality rate, reported in 1897, was representative of the results achieved during this period.[18] Improvements in operative technique and perioperative care during the next quarter century would increase the number of conditions manageable by bilioenteric anastomosis and improved overall results.

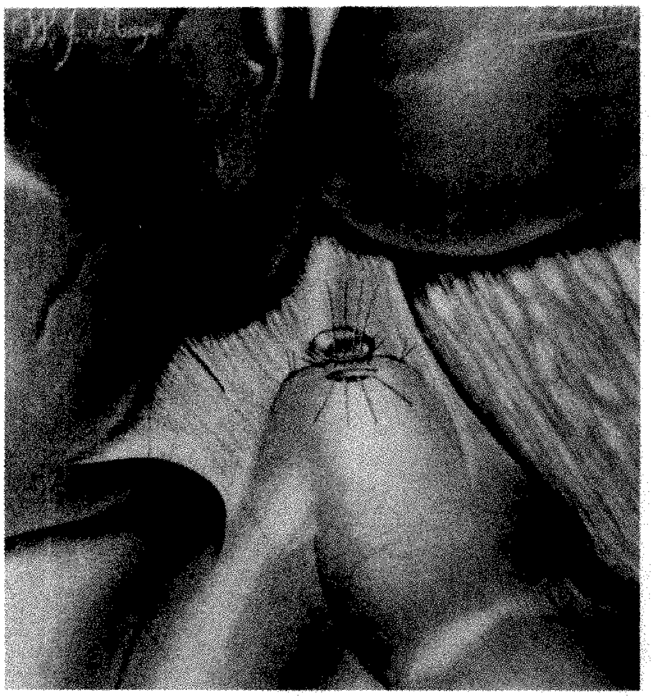

Fig 2.—Mayo's initial hepaticoduodenostomy as described in 1904. Fixation sutures are tied, the duodenum is incised, and the posterior row of through-and-through sutures are put in place (from Mayo[30]).

ADVANCES IN SURGICAL TECHNIQUES

During the early 20th century, operations were introduced for fistula implantation and the creation of an indirect bilioenteric anastomosis by bridging a ductal defect with a stent. Initially, these procedures were popular, but they eventually fell into disfavor. The technique for direct mucosa-to-mucosa anastomosis improved with its increased use in difficult-to-manage, proximal bile duct strictures. A variety of biliary stents were also introduced. Perhaps most importantly, improvements in perioperative care, such as the introduction of blood transfusions and the recognition of the role of calcium in blood clotting, led to marked improvements in survival.

Biliary Fistula Implantation

The frequent establishment of externally draining biliary fistulas after cholecystostomy or unrecognized bile duct injury led to attempts at recreating bilioenteric continuity through implantation of the fistulous tract into the stomach or duodenum. Surgeons quickly recognized that a complete external fistula resulted in malnutrition and, sometimes, death. Moreover, the presence of adhesions from previous surgery or inflammatory conditions made exposure of the proximal biliary tract difficult and time-consuming. Poor anesthetic techniques, limited circulatory support, and coagulopathy in these jaundiced patients necessitated the development of simpler, faster procedures for reconstructing the biliary tract.

In 1902, Vincenz Czerny, Professor of Surgery at Heidelberg (Germany) University, and Billroth's former first assistant, described a cholangiohepatoenterostomy that included the first use of an external biliary fistula in reconstructing the

Table 2.—Early Modification in Technique

Year	Investigator	Fistula Implantation
1902	Czerny[8]	Cholangio-fistula-jejunostomy
1909	Mariani[8]	Cholecysto-fistula-gastrostomy
		Stent Implantation
1910	Jenckel[49]	Hepatico-stent-duodenostomy
1912	Wilms[50]	Choledocho-stent-duodenostomy
		Further Modifications
1900	Pendl[63]	Retrocolic cholecystojejunostomy
1904	Monprofit[65]	Roux-en-Y cholecystojejunostomy
1905	Moynihan[66]	Proximal enteroenterostomy (omega loop)
1909	Dahl[67]	Roux-en-Y hepaticojejunostomy

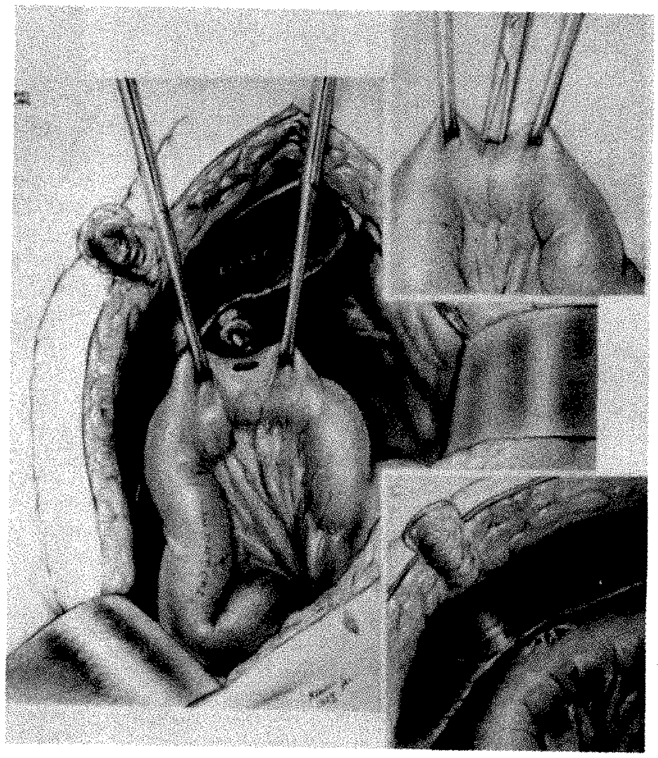

Fig 3.—Lahey's technique of fistulojejunostomy as published in 1929. Preparation of a jejunal loop is demonstrated in the inset at upper right. The fistulous tract was excised, cannulated with a rubber tube, and inserted into the jejunal loop. The inset at lower right shows the completed anastomosis (from Lahey[37]).

biliary tract (Table 2). Czerny inserted the fistula into the jejunal defect left by a nonfunctioning cholecystojejunostomy in a patient with metastatic cancer. The patient died several days later.[8] Ludwig von Stubenrauch of Munich, Germany, attempted a similar procedure several years later. However, the fistulous tract necrosed, and the connecting channel never functioned.[8] Success was finally achieved in Italy by Carlo Mariani in 1909 with a gallbladder fistula that he transplanted into the pylorus, bypassing an occluded common bile duct.[8] In the United States, Williams and Smithwick[33] reported in 1929 the 14-year follow-up of a similar case of an anastomosis between an external biliary fistula and the duodenum.

Enthusiasm for fistula implantation grew during the 1920s, with some surgeons advocating it for cases of common bile duct obstruction.[33] In 1924, Frank Lahey described a case of successful fistula implantation from his early experience with biliary tract strictures (Fig 3). He stressed the importance of carefully preserving the tract down to, but not into, the liver, leaving its blood supply intact.[34-36] He believed that the secretory pressure of bile exceeded the contractility of the granulation tissue surrounding the fistula; thus, the fistula should remain permanently open when implanted internally.[35,37] Both Lahey[38] and Walters[39] recommended this procedure as a simple method for draining the biliary tract when a normal segment of proximal hepatic duct was absent. Several authors reported rapid epithelialization of the sinus tract that they believed would prevent its contraction and the resulting sequela of biliary obstruction.[34,40] In 1922 and 1923, Hildebrandt[41] and von Stubenrauch[42] suggested simplifying the procedure by implanting the fistula subcutaneously in a defunctionalized jejunal limb, although Sutton[43] had unsuccessfully used this technique in 1910.

Initial enthusiasm for fistula implantation waned, however, as longer follow-up revealed a high incidence of recurrent biliary obstruction.[44] By 1936, Lahey[45] performed fistula implantation as a last resort, calling it a makeshift procedure bound to be followed by many failures. In his 1950 summary of the management of 229 bile duct strictures, Lahey[46] added that 86% of his fistula implants had failed, leading him to abandon the procedure.

Wilms-Sullivan Stent Operation

Difficulties in obtaining a tension-free, mucosa-to-mucosa union in cases of common bile duct obstruction or division after cholecystectomy also led to the development of the indirect bilioenteric anastomosis. In 1909, Arthur G. Sullivan[47] of New York, NY, described a series of experiments performed in eight dogs in which the defect between the divided common duct and duodenum was bridged with a rubber tube. The proximal end of the tube was sutured in place in the divided duct, while the distal end was obliquely inserted into the anterior duodenal wall after passing through a 2-cm serosal tunnel, as in a Witzel gastrostomy. The exposed tube was covered with omentum. A sponge attached to the tube in the duodenal lumen advanced the tube with peristalsis such that the tube would pass in 1 week. The dogs were well for as long as 3 years after the procedure, and mucosal growth into the artificial duct was demonstrated histologically at autopsy.[48]

In 1910, Adolf Jenckel,[49] in reporting the experience of the Göttingen (Germany) Clinic, described the 5-year follow-up results of an indirect hepaticoduodenostomy. He inserted one end of a rubber tube that was the size of his little finger into the common hepatic duct of a patient who had undergone cholecystectomy. He tunneled the other end into the duodenum through a Witzel fistula.[8] This patient was well 30 years later.[34] In 1912, Max Wilms,[50] of Heidelberg University, described five cases of indirect bilioenteric anastomosis. However, he recommended its use only in exceptional cases, such as unstable patients, because of how quickly it could be performed. He also described the possibility of stent migration and advocated making the defect as short as possible to allow rapid epithelialization of the ensuing tract. In the United States, Mann[51] and Erdmann[52] soon described cases of successful indirect bilioenteric anastomosis without substantial follow-up. Initial attempts by George Brewer and Frederick Lange, however, resulted in death.[48,53,54]

Despite the initially optimistic results, it soon became evident that the Wilms-Sullivan procedure, like biliary fistula implantation, produced good temporary results in a few very difficult cases, but had unsatisfactory long-term results.[27,32,34,55,56] Lahey and Pyrtek[46] reported a patency rate of only 20% with indirect bilioenteric anastomoses, stating that the general tendency of such implanted tubes was to become plugged in from 1 to 2 years and that strictures occurred after tubes had passed. The ensuing biliary obstruction resulted in frequent incidences of cholangitis and hepatic abscess and a cumulative mortality rate of 29%.

Plastic Conduit Repairs

Biliary diversion using the entire gallbladder or conduits created from serosal or full-thickness flaps were also made during the early 20th century. Initially introduced by Halsted, von Stubenrauch, Walton, and Kehr, these so-called plastic repairs used the gallbladder or gastric, duodenal, and gallbladder flaps or tubes to cover or bridge ductal defects.[8,26,57] These methods, however, were useful only in rare situations, and their widespread use was never adopted.[58,59]

Approaches using other tissues to bridge ductal defects soon followed. Preservation of Oddi's sphincter was considered important in preventing the cycle of reflux, cholangitis, and stricture formation. Segments of artery, vein, fascial tubes, appendix, skin tubes, preserved bile duct, ureter, and small bowel were all used in attempts to reestablish bilioenteric continuity. Most of these tubes gave promising results initially, but, with the exception of small bowel, strictures eventually occurred, and none withstood the test of time.[60-62]

Roux-en-Y Hepaticojejunostomy

Retrocolic cholecystojejunostomy was introduced in 1900 by Pendl[63] at the Allgemeine Krankenhaus in Vienna, Austria, and later by Brentano[64] in Berlin, Germany (Table 2). This technique provided easier approximation of a jejunal loop or, later, a Roux-en-Y limb, to the gallbladder through a defect in the transverse mesocolon. In 1904, Ambrose Monprofit of Angers, France, used the Y anastomosis of César Roux in constructing a cholecystojejunostomy. Monprofit predicted that this technique would prevent the reflux of intestinal contents into the gallbladder, avoiding the complication of ascending cholangitis.[65] Robson's pupil, Berkeley Moynihan, soon advocated using either a Roux-en-Y loop or a jejunal loop with a proximal enteroenterostomy (omega loop) to prevent the reflux of intestinal contents into the gallbladder.[66] In 1909, Robert Dahl[67] of Stockholm, Sweden, used a Roux-en-Y jejunal limb in constructing a hepaticojejunostomy to manage a common hepatic duct fistula. Since its inception, Dahl's technique has been widely used, since it safely bypasses most extrahepatic strictures or ductal defects (Fig 4).

Use of the Roux-en-Y limb made tension-free anastomosis nearly always possible between the gut and any segment of the biliary tree. Thus, isolating an adequate length of bile duct became the limiting factor in achieving a patent anastomosis. Techniques for creating bilioenteric union to short segments of hilar bile ducts were introduced by several authors in the 1940s. Allen[68] inverted the proximal end of a Roux limb and sutured it to the scar tissue surrounding a stump of bile duct at the porta hepatis. Cole et al[69,70] used Hoag's technique[71] in creating a mucosal sleeve in the end of a Roux-en-Y jejunal limb to ensure mucosa-to-mucosa union at the hepatic hilum. In 1969, Smith[72] described a similar technique that created a mucosal graft over a Y-tube. He later adapted the mucosal grafting technique for use with transhepatic stents. This technique permitted retraction of a jejunal mucosal sleeve into the intrahepatic ducts, avoiding union with the scar tissue at the hilum.[73] In 1960, using a different approach, Kirtley[74] widely opened, or fish-mouthed, the proximal common hepatic duct, tacking it to the thickened Glisson's capsule. A Roux-en-Y limb was sutured around, but not to, the open-ended duct. Long-term follow-up revealed patency in 88% of patients in whom this technique had been performed, despite the absence of mucosa-to-mucosa sutures.[75]

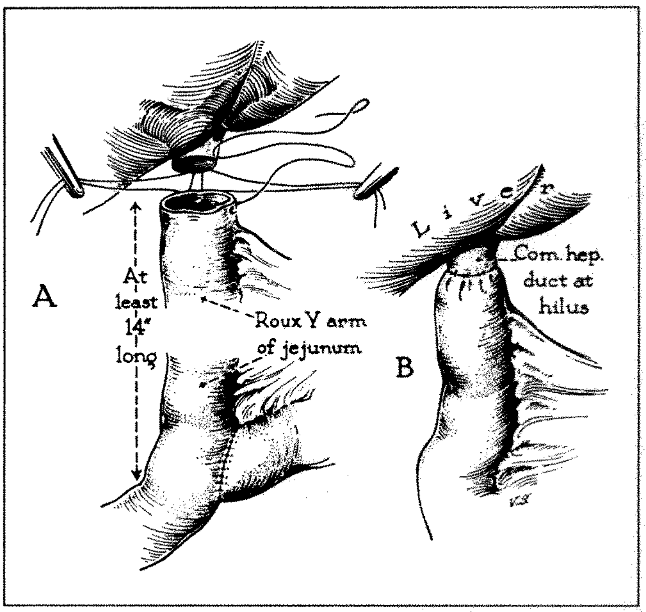

Fig 4.—Construction of a Roux-en-Y hepaticojejunostomy as described by Cole et al (from Cole et al[70]).

Table 3.—Development of Cholangiojejunostomy

Year	Investigator	Cholangioenterostomy
1904	Kehr[76]	Hepatocholangioduodenostomy
1948	Longmire and Sanford[78]	Cholangiojejunostomy
1951	Dogliotti[80]	Cholangiogastrostomy
1956	Hepp and Couinaud[83]	Cholangiojejunostomy
1957	Soupalt and Couinaud[84]	Segment III cholangiojejunostomy, round ligament approach

Cholangioenterostomy

Extensive obstruction of the biliary tree after multiple attempts at repair had long been a nearly insurmountable problem. Absence of a segment of extrahepatic bile duct required establishing continuity between an intrahepatic bile duct and the gut. Such procedures were first envisioned by Baudoin in 1896 and Langenbuch in 1897 and first carried out by Kehr in 1904 (Table 3).[76,77] Kehr created a 6 × 3-cm elliptical defect in the undersurface of the liver with a Pacquelin cautery, opening several larger bile ductules in the process. He then anastomosed a 6-cm segment of adjacent duodenum to the liver capsule surrounding the hepatic defect, creating a hepatocholangioduodenostomy.[76] Despite initial resolution of her jaundice, the patient died 8 weeks later.[3] However, long-term anastomotic patency was rarely achieved, leading Walzel[27] and Graham et al[55] to declare the operation obsolete in the 1920s.

Establishing direct mucosa-to-mucosa continuity between an intrahepatic duct and the gut was the necessary step in achieving lasting drainage of the intrahepatic biliary tree in hilar strictures. Several techniques for exposing segments of the left hepatic duct have been described. In 1948, Longmire and Sanford[78] described an intrahepatic cholangiojejunostomy. A large intrahepatic duct was exposed by resecting a wedge of the left lobe of the liver. They subsequently performed an end-to-side anastomosis between the intrahepatic duct and a jejunal loop with a proximal enteroenterostomy (Fig 5).[79] In 1951, Dogliotti,[80] of Turin, Italy, described a similar technique of left hepatic resection followed by end-to-side anastomosis of an intrahepatic duct to the lesser curva-

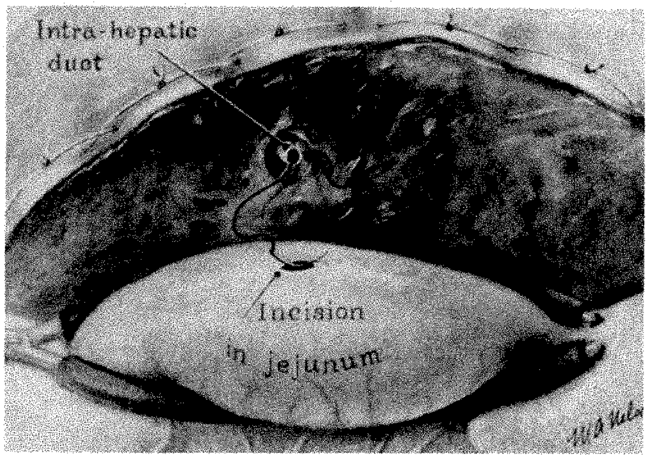

Fig 5.—Intrahepatic cholangiojejunostomy as described by Longmire and Sanford. The end of the intrahepatic duct is sutured to an incision in the side of the jejunal loop (from Longmire and Sanford[78]).

ture of the stomach, creating an intrahepatic cholangiogastrostomy. In five cases performed between 1946 and 1954, he reported great success with this technique.[81]

Additional techniques of intrahepatic cholangiojejunostomy were based largely on Couinaud's studies of segmental hepatic anatomy.[82] Hepp and Couinaud[83] exposed the left main hepatic duct at the base of the quadrate lobe (segment IV), permitting a long side-to-side cholangiojejunostomy in unscarred tissue. Soupault and Couinaud[84] described the round ligament approach to the hepatic duct in segment III of the liver in 1957. Left-sided cholangiojejunostomy is technically easier than right intrahepatic anastomosis and, in the majority of cases, provides satisfactory decompression. However, atrophy of the left lobe or cholangitis resulting from an occluded right hepatic duct occasionally requires a right cholangiojejunostomy or bilateral anastomoses.[85,86] Wedge resection and exposure of the duct to segment V for right-sided cholangiojejunostomy and resection of the quadrate (segment IV) lobe for bilateral cholangiojejunostomy have also been described.[85,86] Encouraging results have been achieved using these techniques in high bile duct strictures.[86,87]

Further modifications have been added to the standard bilioenteric anastomosis in recent years. An increased incidence of peptic ulcer disease after hepaticojejunostomy has been described by several authors.[88,89] The successful use as early as 1915 of jejunal interposition grafts to bypass ductal defects in dogs led McArthur and Longmire to propose jejunal interposition choledochoduodenostomy in 1971.[60-62,89,90] Seven years later, Wheeler and Longmire[91] reported a decreased incidence of peptic ulcers after long-term follow-up in patients who had undergone hepatojejunoduodenostomy.[91] However, the relatively infrequent incidence of peptic ulcers in most series of hepaticojejunostomies and the potentially increased morbidity of an additional duodenal suture line have prevented the widespread use of this procedure.[92-94] Increased use of fiberoptic endoscopy and percutaneous access to the biliary tree for diagnosis and treatment have led to additional modifications in operative procedures. The Roux-en-Y hepaticojejunostomy is inaccessible to the endoscope in its traditional form. Creation of a stoma in the jejunal limb proximal or distal to the bilioenteric anastomosis or fixation of the limb to the posterior rectus fascia provides access to the anastomosis.[95-97]

Biliary Stents

A wide variety of transanastomotic biliary stents have been used since Terrier[15] reported the use of a rubber tube in 1890.

Table 4.—Evolution of Biliary Stents

Year	Investigator	Stent
1890	Terrier[15]	Straight
1894	Murphy[98]	Button
1912	Kehr[19]	T-tube
1923	McArthur[100]	Cuffed tube
1942	Lahey[101]	Y-tube
1951	Goetze[107]	Transhepatic

Stents have been used to provide biliary drainage and prevent cicatricial contraction at a bilioenteric anastomosis and have been especially useful when mucosa-to-mucosa union has been impossible. In 1894, Murphy[98] described an 11-minute cholecystoduodenostomy in which a button was used to aid in the rapid and simple construction of an anastomosis (Table 4). He supported the use of his button by claiming a 34% mortality rate in patients with sutured anastomoses compared with an 8% mortality rate in patients who had undergone the button technique. The two halves of the Murphy button were inserted into the gallbladder and duodenum and held in place by purse-string sutures. The two ends were then snapped together, forming a union between the two structures. The button stented the anastomosis for a variable period until the intervening tissue sloughed and the button was passed. Kocher, Robson, Pendl, and others also advocated its use.[18,63] Robson used hollow segments of decalcified bone to briefly stent bilioenteric anastomoses until the bone decomposed in several days. Complications with the Murphy button, such as hemorrhage; retention of the button in the biliary tree, leading to recurrent obstruction; and anastomotic stricture following premature passage, led to its widespread abandonment, although Walters continued to support its use as late as 1930.[18,39,99]

Rubber, cobalt-chromium alloy (Vitallium), or silicone tubes in various shapes were used for internal anastomotic stenting since Terrier's initial cholecystoduodenostomy. Vitallium was introduced as a substitute for rubber because of its low tissue reactivity. Bouncing clay or polymeric silicone was later used, offering advantages over tubes of other materials in that it could be readily cast into any shape.[46] However, straight, indwelling tubes had several drawbacks, including premature dislodging after several days, especially if one end was exposed to the peristaltic action of the alimentary tract. This situation predisposed to early restricturing at the anastomosis.[34,46]

Several modifications were introduced to permit prolonged use of internal stents. In 1923, McArthur[100] reported using a long rubber tube with a reversed cuff in the end that he placed in the bile duct proximal to a hepatoduodenostomy (Table 4). The cuff allowed the rubber tube to resist the peristaltic pull of the duodenum, controlling the length of stenting. The Y-tube was initially employed at the Lahey Clinic, Boston, Mass, in 1942. The Y-tube had two diverging limbs that were placed in the main hepatic ducts and a vertical limb for the common duct or jejunum. With the suggestion that longer periods of stenting provided superior results, the Y-tube became the preferred internal stent, because it often remained in place for years.[101,102]

In the 1950s, Vitallium tubes were modified to include a flange that protruded through the anastomosis, securing it in place.[103] However, rigid Vitallium tubes were often difficult to insert into angular segments of the biliary tree and occasionally eroded into the duodenum, causing hemorrhage, perforation, and death.[46] Both the Y- and Vitallium tubes often remained in place for years and became encrusted with sludge, leading to recurrent cholangitis. This situation frequently required reoperation for removal or replacement of the tube.[34,56] In the 1960s, Warren reported that the use of these stents for proximal duct strictures required reoperation for the removal of an occluded stent in approximately 50% of patients.[101,102]

Tubes were also used to provide external drainage after surgery. In 1902, Robson[25] described the use of the straight rubber Nélaton catheter after choledochotomy as a stent and as a method for external drainage. A biliary tube with an external limb supplied a means of tube removal and allowed control of the stenting period. In 1911, Voelcker[104] described a technique for stenting a bilioenteric anastomosis in which a rubber tube was used to stent a hepatoduodenostomy through a separate duodenal Witzel fistula and the abdominal wound. Although an improvement, this technique created the potential for a persistent duodenal fistula and left the stent exposed to the peristaltic action of the small bowel. In 1912, Kehr introduced the T-tube as a method for both stenting the common bile duct after choledochotomy and providing external drainage.[23] The T-tube has subsequently been used in a variety of bilioenteric anastomoses, although it is most effective when the external limb is brought out proximal to the anastomosis.[8,105]

In 1950, Lahey introduced a modification of the T- and internal Y-tubes for proximal common bile duct strictures. His modified stent provided short proximal arms for both major intrahepatic ducts, a long vertical limb for the common hepatic duct, and a limb for external drainage and access to the biliary tree.[46] In 1972, Warren et al[106] described a modified Y-tube in which a solid external limb was created to prevent precipitation in the stagnant-side limb from causing occlusion of the internal portion of the stent.

Transhepatic intubation of the biliary tree for the management of benign and malignant strictures was initially described by several authors, including Goetze and Praderi.[23,107,108] In 1951, Goetze[107] exteriorized the proximal end of a long rubber tube through the parenchyma of the right hepatic lobe and brought the opposite end through a Witzel fistula in a Roux limb 15 cm distal to a hepaticojejunostomy (Table 4). He later concluded that transhepatic stents reliably prevented early anastomotic stricturing, could be securely held in place for prolonged periods, and could be removed or changed easily.[109] The technique was popularized in the English literature by Smith.[110] Further experience with long-term transhepatic stenting has established it as a valuable technique.[108]

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In mixed infections

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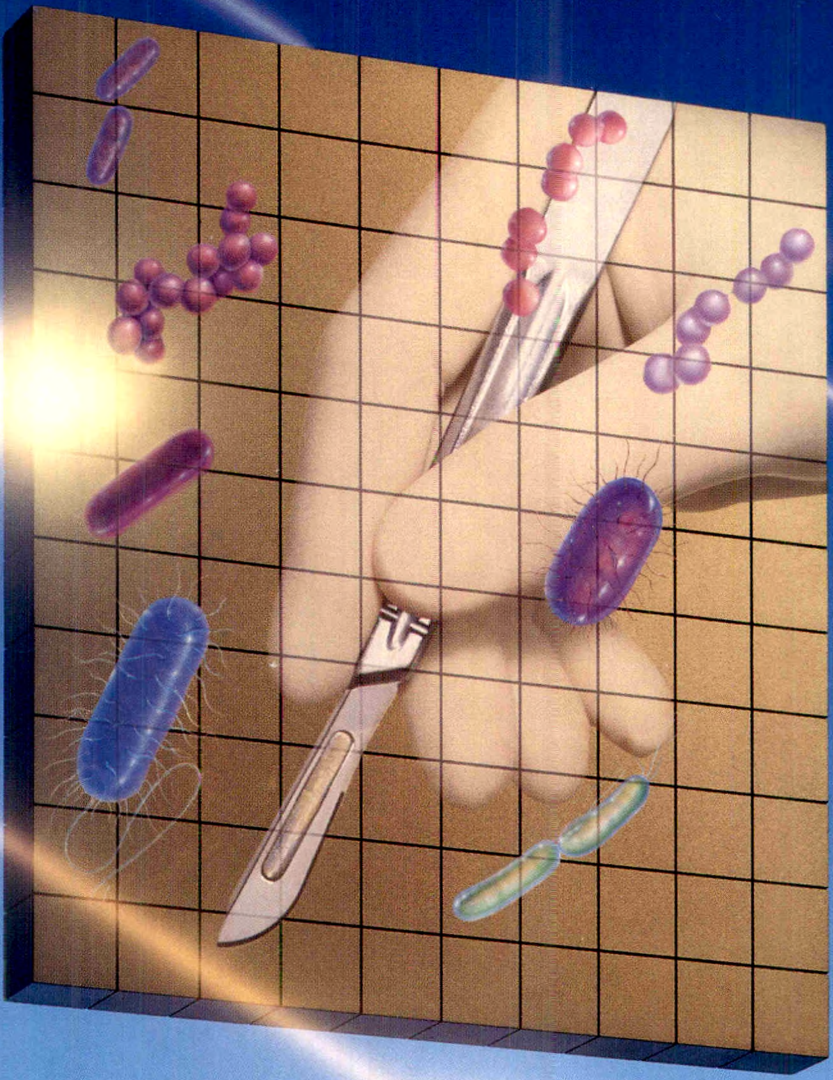

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- Single-agent convenience

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In vitro activity does not necessarily imply *in vivo* efficacy.
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BRIEF SUMMARY OF PRESCRIBING INFORMATION

TIMENTIN® **sterile ticarcillin disodium and clavulanate potassium** for Intravenous Administration

INDICATIONS AND USAGE: TIMENTIN™ is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Bacterial Septicemia: including bacteremia, caused by ß-lactamase producing strains of *Klebsiella* spp., *E. coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* (and other *Pseudomonas* species). Lower Respiratory Infections: caused by ß-lactamase producing strains of *Staphylococcus aureus*, *Hemophilus influenzae* and *Klebsiella* spp. Bone and Joint Infections: caused by ß-lactamase producing strains of *Staphylococcus aureus*. Skin and Skin Structure Infections: caused by ß-lactamase producing strains of *Staphylococcus aureus*, *Klebsiella* spp., and *E. coli*. Urinary Tract Infections (complicated and uncomplicated): caused by ß-lactamase producing strains of *E. coli*, *Klebsiella* spp., *Pseudomonas aeruginosa* (and other *Pseudomonas* species), *Citrobacter* spp., *Enterobacter cloacae*, *Serratia marcescens*, and *Staphylococcus aureus*. Gynecologic Infections: Endometritis caused by ß-lactamase producing strains of *B. melaninogenicus*; *Enterobacter* spp. (including *E. cloacae**), *Escherichia coli*, *Klebsiella pneumoniae*,* *Staphylococcus aureus*, and *Staphylococcus epidermidis*.

While TIMENTIN is indicated only for the conditions listed above, infections caused by ticarcillin susceptible organisms are also amenable to TIMENTIN treatment due to its ticarcillin content. Therefore, mixed infections caused by ticarcillin susceptible organisms and ß-lactamase producing organisms susceptible to TIMENTIN should not require the addition of another antibiotic.

ADVERSE REACTIONS: As with other penicillins, the following adverse reactions may occur: *Hypersensitivity reactions:* skin rash, pruritus, urticaria, arthralgia, myalgia, drug fever, chills, chest discomfort, and anaphylactic reactions. *Central nervous system:* headache, giddiness, neuromuscular hyperirritability or convulsive seizures. *Gastrointestinal disturbances:* disturbances of taste and smell, stomatitis, flatulence, nausea, vomiting and diarrhea, epigastric pain. *Hemic and Lymphatic systems:* thrombocytopenia, leukopenia, neutropenia, eosinophilia and reduction of hemoglobin or hematocrit. Prolongation of prothrombin time and bleeding time. *Abnormalities of hepatic and renal function tests:* elevation of serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), serum alkaline phosphatase, serum LDH, serum bilirubin. Rarely, transient hepatitis and cholestatic jaundice–as with some other penicillins and some cephalosporins. Elevation of serum creatinine and/or BUN, hypernatremia. Reduction in serum potassium and uric acid. *Local reactions:* pain, burning, swelling and induration at the injection site and thrombophlebitis with intravenous administration. *Overdosage:* As with other penicillins, TIMENTIN in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures. Ticarcillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding and pharmacokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by hemodialysis.

CONTRAINDICATIONS: TIMENTIN is contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH TIMENTIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER DRUGS. IF AN ALLERGIC REACTION OCCURS, TIMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE PROVIDED AS INDICATED.**

PRECAUTIONS: While TIMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, organ system functions should be assessed periodically during therapy.

Bleeding manifestations have occurred in some patients receiving ß-lactam antibiotics. These reactions have been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal impairment. If bleeding manifestations appear, TIMENTIN treatment should be discontinued and appropriate therapy instituted.

TIMENTIN has only rarely been reported to cause hypokalemia. Periodic monitoring of serum potassium may be advisable in patients receiving prolonged therapy.

Pregnancy (Category B): Reproduction studies have been performed in rats given doses up to 1050 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to TIMENTIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

DOSAGE AND ADMINISTRATION: TIMENTIN should be administered by intravenous infusion (30 min.). Usual recommended dose for systemic and urinary tract infections for average (60 kg) adults is 3.1 Gm TIMENTIN (3.1 Gm vial containing 3 Gm ticarcillin and 100 mg clavulanic acid) given every 4 to 6 hours. For gynecologic infections TIMENTIN should be administered as follows: Moderate infections 200 mg/kg/day in divided doses every 6 hours and for severe infections 300 mg/kg/day, based on ticarcillin content, in divided doses every 4 hours. For patients weighing less than 60 kg, the recommended dosage is 200-300 mg/kg/day, based on ticarcillin content, given in divided doses every 4 to 6 hours. In urinary tract infections, a dosage of 3.2 Gm TIMENTIN (3.2 Gm vial containing 3 Gm ticarcillin and 200 mg clavulanic acid) given every 8 hours is adequate. Please see official package insert for details on dosages for other patients, including those with renal insufficiency, and directions for use.

SUPPLIED: 3.1 Gm and 3.2 Gm Standard Vials; 3.1 Gm and 3.2 Gm Piggyback Bottles; 31 Gm Bulk Pharmacy Package; 3.1 Gm ADD-Vantage™ Antibiotic Vial.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections. 7548/H-BS ©1990, Beecham Laboratories

Reference:

1. Data on file, Medical Department, SmithKline Beecham Pharmaceuticals.

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Clinical Notes

The Papillary-Cystic Neoplasm of the Pancreas

An Increasingly Recognized Clinicopathologic Entity

Juan A. Sanchez, MD; Kurt D. Newman, MD; Martin R. Eichelberger, MD; Russell J. Nauta, MD

• The clinical course of the papillary-cystic neoplasm of the pancreas is contrasted with that of the pancreatic ductal adenocarcinoma. The former occurs predominantly in young women, has a low malignant potential, and is highly curable with surgical treatment. Three cases are reported that illustrate the typical clinical features and the indolent nature of the tumor. One case was discovered after blunt abdominal trauma resulted in rupture of the tumor and hemoperitoneum. All cases were treated by pancreatic resection with preservation of the spleen, an important consideration in younger patients. All patients were free of disease at long-term follow-up. Increasing awareness of this tumor has resulted in the reclassification of several tumors and should lead to better recognition by surgeons caring for patients with pancreatic diseases.

(*Arch Surg.* 1990;125:1502-1505)

Ductal adenocarcinoma is the most common neoplasm arising from the pancreas. Usually seen in patients in their fifth and sixth decades of life, it has a distinct male predilection and carries a poor prognosis despite all forms of therapy. In contrast, the papillary-cystic tumor of the pancreas seems to affect women almost exclusively, particularly in their second and third decades of life. Increasing awareness of this entity has resulted in the reclassification of several tumors previously misdiagnosed as cystic islet cell tumors and other pancreatic neoplasms. Three cases are reported, along with the salient clinicopathologic features of this tumor. Surgeons encountering papillary-cystic tumors of the pancreas should recognize their low malignant potential and their high curability with surgical treatment.

REPORT OF CASES

CASE 1.—A 21-year-old black woman was examined for a 6-month history of intermittent midepigastric pain and progressive epigastric fullness. She denied weight loss, anorexia, and changes in bowel habits but noted increased fatigue. She denied previous abdominal trauma, and her medical history was otherwise unremarkable.

On physical examination, a large, firm, nontender mass was palpable in the epigastrium. Normal bowel sounds were present. The liver was not enlarged, and no other abdominal masses were noted. The patient was anicteric, and the remainder of the physical examination showed nothing abnormal. Her chemical and hematologic profiles were normal, including the serum bilirubin level.

A plain abdominal roentgenogram and an upper gastrointestinal tract series demonstrated the displacement of the transverse colon by a space-occupying lesion in the upper abdomen. Visceral angiography showed shifting of vessels by the large mass but was otherwise unremarkable. A computed tomographic (CT) scan was obtained (Fig 1), demonstrating a large cystic mass involving the head and body of the pancreas. An endoscopic retrograde cholangiopancreatogram was performed to define the ductal anatomy and showed displacement of the pancreatic duct by the mass (Fig 2).

At celiotomy, a large mass arising from the pancreas was confirmed. There appeared to be no invasion of surrounding structures. A pancreatoduodenectomy (Whipple's procedure) was performed with complete excision of the tumor (Fig 3). The mass measured 15 cm in diameter and, on sectioning, 1.6 L of dark fluid was evacuated from its cystic cavity. The lining of the cavity was irregular and contained firmly adherent clots. Histologic sections showed layers of uniform-appearing cells arranged in papillary fashion as well as several foci of hemorrhage coalescing into areas of cystic degeneration with irregular walls. A rim of compressed pancreatic tissue was detected between the tumor and the ampullary region of the duodenum. There was no indication of invasion of surrounding fibrovascular capsule by the tumor. Immunoperoxidase reactions for insulin, serotonin, glucagon, corticotropin, and carcinoembryonic antigen were negative. The neuron-specific enolase reaction was weakly positive.

Based on the available clinical and pathologic data, a diagnosis of papillary-cystic neoplasm of the pancreas was made. Her postoperative convalescence was unremarkable. The patient has been followed up for 3 years by serial abdominal examinations and CT scans and has had no detectable recurrence.

CASE 2.—A 14-year-old girl was examined for a 7-day history of abdominal pain and nausea. Physical examination revealed a large, tender, left upper quadrant abdominal mass separate from the spleen. A CT scan of the abdomen showed a 15 × 15-cm cystic mass in the distal pancreas. There was no evidence of distant metastases on preoperative studies.

She underwent surgical exploration and was found to have a large mass in the distal pancreas. The pancreas was resected distal to the superior mesenteric vessels. The spleen was preserved. The patient

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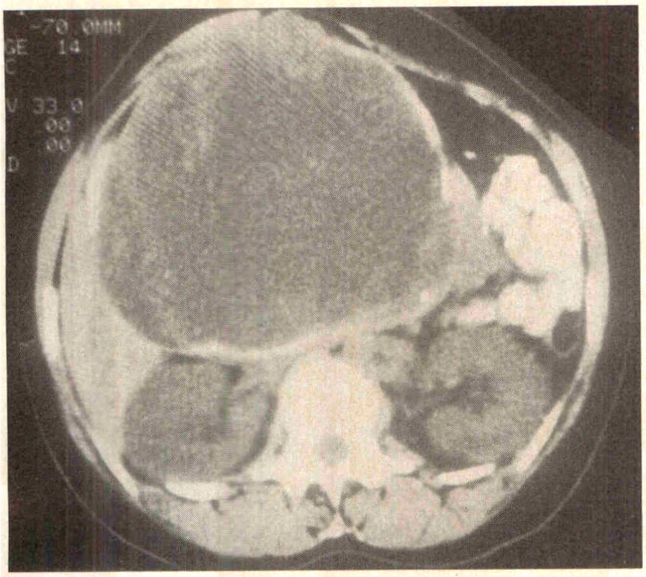

Fig 1.—Case 1. An abdominal computed tomographic scan shows a large cystic mass involving the head and body of the pancreas.

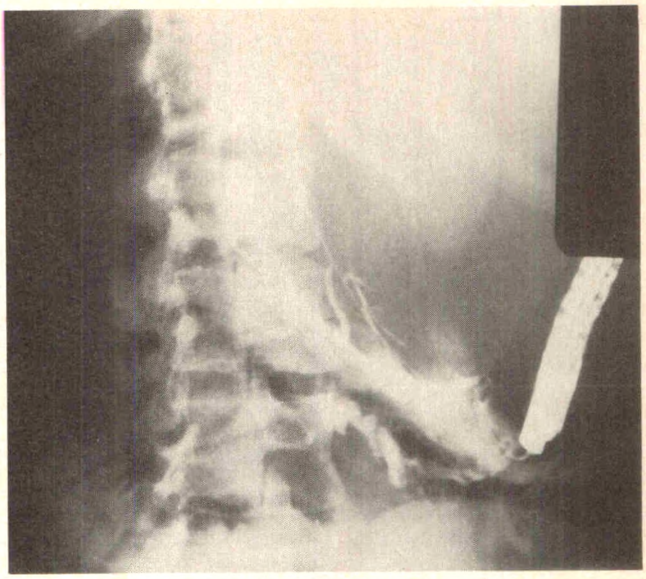

Fig 2.—Case 1. Endoscopic retrograde cholangiopancreatography demonstrates splaying of the main pancreatic duct, with secondary ducts coursing through the substance of the mass.

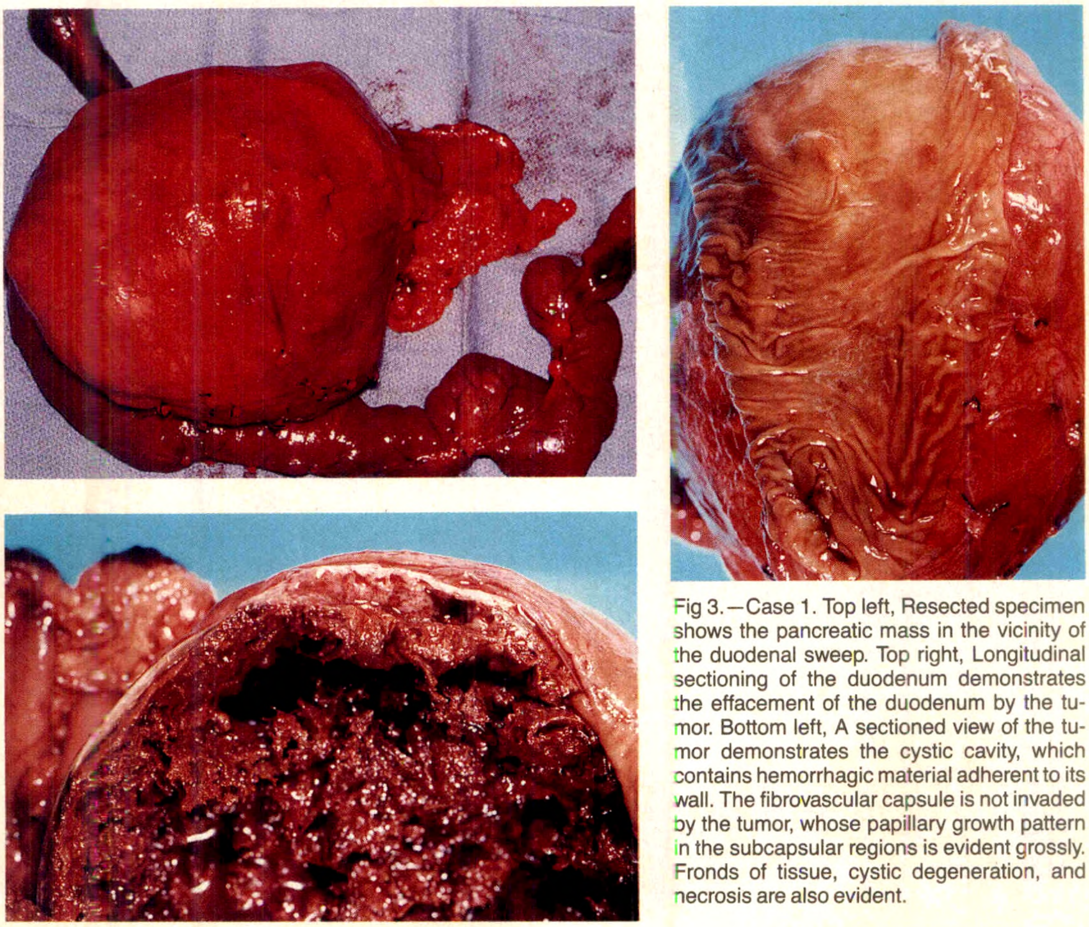

Fig 3.—Case 1. Top left, Resected specimen shows the pancreatic mass in the vicinity of the duodenal sweep. Top right, Longitudinal sectioning of the duodenum demonstrates the effacement of the duodenum by the tumor. Bottom left, A sectioned view of the tumor demonstrates the cystic cavity, which contains hemorrhagic material adherent to its wall. The fibrovascular capsule is not invaded by the tumor, whose papillary growth pattern in the subcapsular regions is evident grossly. Fronds of tissue, cystic degeneration, and necrosis are also evident.

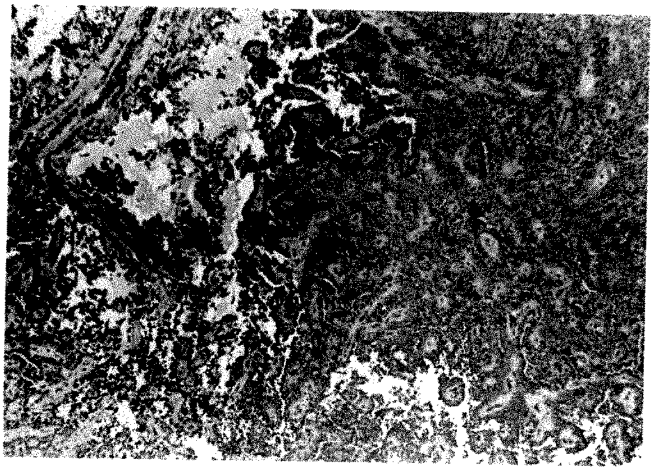

Fig 4.—Case 2. Light microscopic slide shows distinctive features of papillary-cystic neoplasm: sheets of well-differentiated cells on a fibrovascular stalk, with hemorrhage (hematoxylin-eosin, original magnification × 140).

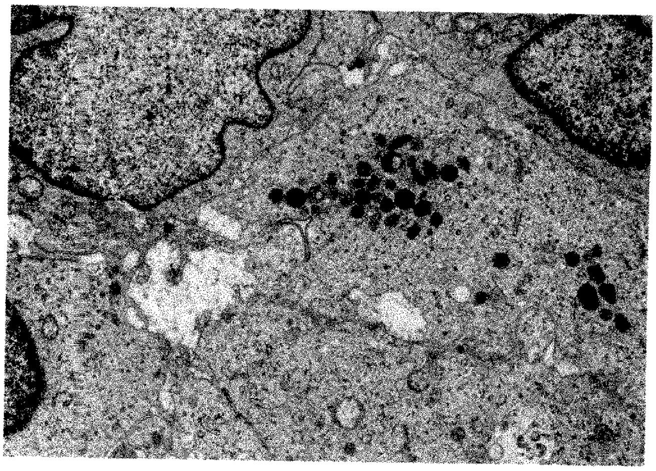

Fig 5.—Case 3. Electron microscopic view shows acinar differentiation with cells arranged about a central pale lumen and abortive microvillus formation. Neurosecretory granules, located centrally, are suggestive of pluripotent cell lineage.

recovered from the procedure uneventfully. Pathologic examination of the specimen demonstrated a papillary-cystic neoplasm of the pancreas with margins free of tumor (Fig 4). At 4 years' follow-up, she remains clinically and roentgenographically free of recurrent disease.

CASE 3.—A 13-year-old girl was struck on her left side while wrestling at a party. She was seen at another hospital, where she became hypotensive. After resuscitation with crystalloid solution and 2 U of blood, she was transferred to Childrens Hospital National Medical Center, Washington, DC. On physical examination, she had marked abdominal distention and tenderness. An abdominal CT scan showed a large mass in her distal pancreas.

At celiotomy, a large, hemorrhagic mass measuring approximately 10 cm in diameter was found in the distal pancreas without extension to other organs. A distal pancreatic resection was performed, and the spleen was preserved. Her postoperative course was unremarkable. Pathologic examination of the surgical specimen showed a papillary-cystic neoplasm of the pancreas (Fig 5). Although the tumor had ruptured, resulting in hemoperitoneum, the resection margins were free of disease and, at 4 years, she is clinically free of recurrent disease.

COMMENT

The papillary-cystic tumor of the pancreas is a rare and unique clinicopathologic entity that has only recently received attention. Though first described as a "papillary tumor of the pancreas" by Frantz[1] in 1959, subsequent reports of this lesion have surfaced under various different names. The terms *solid and papillary, papillary epithelial*, and others noting its singular microscopic appearance have been employed in describing this tumor. More recently, investigators have focused on the ultrastructural and immunohistochemical features in an attempt to delineate its cell of origin.[2] Although fewer than 120 cases are reported in the literature, many of these newer reports include cases that, while originally misdiagnosed, have been reevaluated in light of greater awareness of the existence of this tumor. Based on this observation,[3] it is conceivable that the actual incidence of the papillary-cystic tumor is much greater than anticipated.

The tumor is seen in patients in their second and third decades of life, with a mean age of 22 years. Most cases have occurred in female patients, and more than half of the patients have been 18 years old or younger. There also seems to be a racial predilection, with almost half of the cases occurring in blacks. These demographics are in contradistinction to the commonly encountered adenocarcinoma of the pancreas, which is seen more commonly in men in their later decades of life, although it also appears to have a predilection for blacks.[4,5]

Most patients describe a slowly enlarging, nontender, upper abdominal mass. Many patients are completely asymptomatic, however, and the lesions are detected either after surgical evaluation for unrelated conditions or at autopsy.[6] Rupture of the tumor with hemoperitoneum brought attention to its presence in one of our patients as well as in one other reported case.[3] Abdominal pain, though present in only 25% of patients, is the second most common complaint.[6]

On physical examination, a large, smooth mass is usually palpable in the upper abdomen, commonly in the left upper quadrant. The mass appears fixed to the retroperitoneum and is not tender. Jaundice is rare, even in tumors that originate from the head of the pancreas, as in patient 1. No other abnormalities on examination are typically found.

The diagnosis of the papillary-cystic tumor may be suggested by its appearance on various imaging modalities and is corroborated by the clinical history. Plain abdominal roentgenography may be normal or may show displacement of the normal bowel gas pattern. Despite the slow-growing nature of the tumor and the presence of multiple hemorrhagic areas, calcifications within the large mass are rarely encountered. When present, however, they are peripheral and curvilinear, as compared with the sunburst pattern described for microcystic adenomas.[7] Ultrasonography may identify the cystic and solid components, which are characteristic. However, the most helpful study is the CT scan (Fig 1), which is able to identify the areas of cystic degeneration, helps determine size and configuration of the mass, and defines the pancreatic anatomy as well as the presence of invasion into surrounding structures.

Even in young women, other cystic lesions afflicting the pancreas should be considered. The differential diagnosis includes other neoplasms such as cystadenomas, cystadenocarcinomas, microcystic adenomas, hemangiomas, lymphangiomas, various forms of sarcomas, and the rare cystic islet cell tumors, with which papillary-cystic neoplasms are often confused histologically.[8,9] The cystadenoma and its malignant counterpart may be distinguished by the presence of a cyst wall lined by flat cuboidal or columnar cells, whereas the papillary-cystic neoplasm's capsule is fibrovascular.[10] These lesions, like the papillary-cystic tumor, have a striking female predilection. Whether this represents a hormonal influence is not entirely known. Estrogen and progesterone receptors, not present in the normal pancreas, have recently been detected in the papillary-cystic neoplasm.[11] In islet cell tumors, by contrast, the sex ratio seems to be equal. Functional endocrine tumors may be identified by the detection of elevated levels of insulin, gastrin, somatostatin, serotonin, glucagon, vasoactive intestinal polypeptide, corticotropin, or pancreatic polypeptide. However, endocrine tumors of the pancreas, whether functional or not, are usually solid, even when large, with rare cases of cystic degeneration.[9] Nonneoplastic cystic lesions of the pancreas are quite common and should also be considered.

Fine-needle aspiration biopsy has been recently employed to diagnose these tumors preoperatively. This may be accomplished percutaneously with or without sonographic or CT guidance. This procedure may yield clumps of cell layers showing the singular branching papillary pattern as well as the associated perivascular myxoid material often found within these tumors.[12,13]

Grossly, these broad-based tumors can achieve sizes as large as 20 cm.[6] They are usually vascular and contain numerous areas of hemorrhagic necrosis. Commonly, the mass originates in the tail of the pancreas. On cut section, cystic and solid areas are intermixed, and hemorrhagic fluid is obtained. The blood supply is entirely derived from the pancreas itself.

The histologic appearance varies throughout the different areas of the lesion. The solid component shows sheets of cells that mimic the pattern seen with endocrine neoplasia.[14] Indeed, many such tumors have been classified as a nonfunctional islet cell tumors and have only been reevaluated on the basis of an increased awareness of this entity.[3] However, neurosecretory granules are infrequently identified on electron microscopy, and cystic islet cell tumors, as stated earlier, are rare. Other areas from the same specimen will show the characteristic branching papillary fronds of a fibrovascular stalk, while yet other areas show cystic degeneration, necrosis, and hemorrhage.[15]

The cell of origin of the papillary-cystic neoplasm is elusive. Ultrastructural features have suggested at least partial acinar differentiation, and some investigators have proposed lineage from the cells of the small pancreatic ducts.[11,16] However, neurosecretory granules on electron microscopy have been detected in some cases, and it is postulated that this neoplasm originates from a pluripotent cell.[2,3,17,18]

These tumors are considered malignant because of their potential for invasion of the fibrovascular capsule as well as the ability for metastatic spread. Invasion of the tumor into surrounding structures such as the duodenum and portal vein has been described, but descriptions of tumors exhibiting such "aggressive behavior" are scant.[4,19] Although infrequent, distant metastasis has been reported in the lung, liver, and skin and has been the cause of some deaths.[3] However, complete surgical resection is usually curative, with no long-term recurrences in most cases. Even metastatic disease and local recurrences are amenable to surgical treatment, with good long-term results.[14,16] The surgical approach depends on the location of the lesion. Tumors arising from the tail of the pancreas can be excised by distal pancreatectomy with preservation of the spleen, an important consideration in younger patients. Proximal lesions may require pancreatoduodenectomy, as in patient 1. Complete removal of all tumor, however, is mandatory to achieve a cure.

Recently, radiotherapy has provided complete regression of this tumor in a small number of patients.[20] Although the role of this modality in the treatment of papillary-cystic tumors of the pancreas is unclear, it implies that some tumors may be radiosensitive and suggests the use of radiation in cases of direct invasion where complete extirpation is not feasible.

The dismal course of ductal adenocarcinoma of the pancreas has prompted some to abandon talk of cure and suggest nihilism or palliative bypass as the best operative approach. With 5-year survival rates of 5% to 10%, the prognosis of this more common solid neoplasm must be distinguished from that of the papillary-cystic neoplasm of the pancreas. The latter, occurring primarily in young women, is of insidious onset, behaves indolently, is often resectable, and thus merits careful attention to differential diagnosis and a surgical approach aimed at cure.

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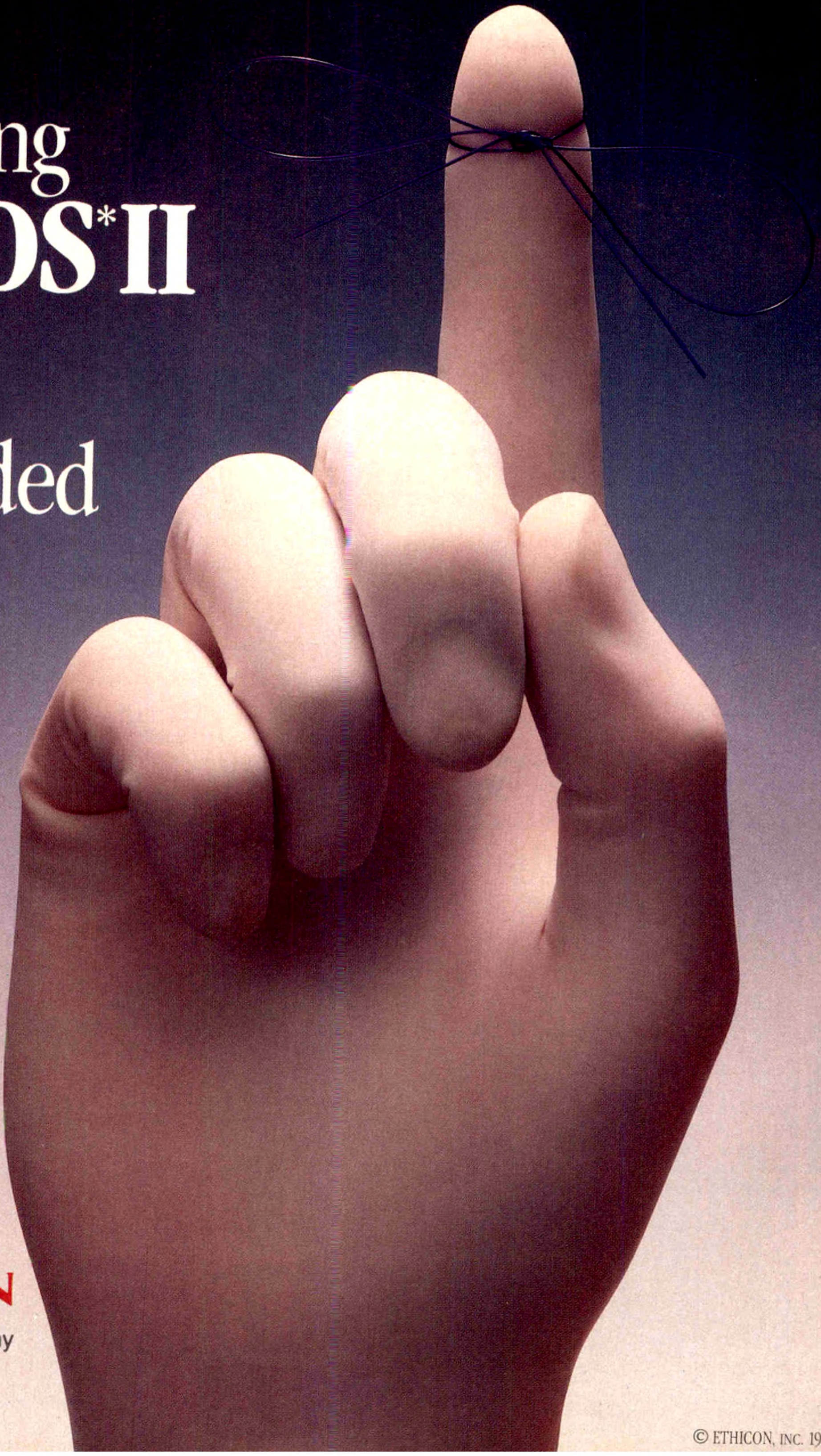

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Extrahepatic Biliary Obstruction by Lymphoma

Edward Feller, MD, Fred J. Schiffman, MD

• Extrinsic compression of the common bile duct by enlarged lymph nodes is an unusual cause of obstructive jaundice. We describe two patients with such a manifestation of lymphoma and the use of endoscopic retrograde cholangiopancreatography in distinguishing this rare complication from other causes of jaundice in lymphoma. Patients may have rapid resolution of both symptoms and biochemical abnormalities by nonoperative biliary bypass combined with chemotherapy and/or radiotherapy. Lymphomatous obstruction should be considered a cause of potentially treatable jaundice in patients with known lymphoma; endoscopic retrograde cholangiopancreatography can be valuable as a diagnostic and therapeutic tool.

(*Arch Surg.* 1990;125:1507-1509)

Lymphomatous obstruction of the extrahepatic biliary system is a rare cause of jaundice and is an unusual manifestation of non-Hodgkin's lymphoma. Most commonly, jaundice in these patients is due to hepatic involvement.[1,2] Less frequently, intrahepatic cholestasis, primary hepatic lymphoma, intercurrent viral infection, or toxic hepatitis due to drug treatment, as well as extrahepatic obstruction, may also occur.[3-5] We have recently seen two patients with known lymphoma who developed severe jaundice due to extrinsic compression of the common bile duct by enlarged lymphomatous lymph nodes. In both cases, endoscopic retrograde cholangiopancreatography (ERCP) was vital for accurate clinical assessment and appropriate individualized management. This report discusses the evaluation and management of the unusual occurrence of extrahepatic obstruction in lymphoma.

REPORT OF CASES

CASE 1.—An 81-year-old woman was admitted to the hospital in October 1985, with jaundice of 1 day's duration. Cholecystectomy for acute cholecystitis had been done in 1984. In May 1985, she had a groin tumor diagnosed as stage IA mixed lymphocytic histiocytic lymphoma. She was treated with 2 mg of chlorambucil daily, with complete resolution until her current admission.

On admission to the hospital, physical examination results were unremarkable except for jaundice. Pertinent laboratory data included the following values: alkaline phosphatase, 660 IU/L (normal, 48 to 122 IU/L); γ-glutamyl transpeptidase, 510 U/L (normal, 8 to 78 U/L); total bilirubin, 212 μmol/L with a direct fraction of 155 μmol/L; and aspartate aminotransferase, 141 IU/L (normal, 13 to 47 IU/L). A computed tomographic (CT) scan of the abdomen (8800 CT-T, General Electric Co, Milwaukee, Wis) demonstrated dilated intrahepatic bile ducts with a mass in the porta hepatis. Endoscopic retrograde cholangiopancreatography (JF-B 1T, Olympus Corp, Lake Success, NY) revealed no filling of the left hepatic duct and a stricture with mass effect of the proximal common bile duct at the origin of the right and left hepatic ducts (Fig 1). Computed tomography–guided percutaneous biopsy revealed lymphoma of the same cell type as the original tumor. A percutaneously placed stent produced drainage of bile. Limited field radiation produced regression of the jaundice and normalization of other liver function abnormalities. She then developed disseminated disease and was treated with chemotherapy but died 6 months later.

CASE 2.—A 61-year-old man was admitted to the hospital in March 1985, with a 10-day history of jaundice without pain or fever. In 1977, excision of an enlarged left inguinal lymph node revealed a well-differentiated stage I lymphocytic lymphoma that resolved completely with chemotherapy and radiotherapy. In 1980, he was readmitted with abdominal pain. Staging evaluation, including laparotomy, revealed a stage III lymphocytic lymphoma, and he was treated with bleomycin sulfate, doxorubicin hydrochloride, cyclophosphamide, and vincristine sulfate for six cycles. He was well until his admission with jaundice. Results of physical examination at that time were unremarkable except for jaundice. Pertinent laboratory data included the following values: alkaline phosphatase, 920 U/L; γ-glutamyl transpeptidase, 980 U/L; aspartate aminotransferase, 218 U/L; and bilirubin, 109 μmol/L (direct) and 144 μmol/L (total). Abdominal ultrasound examination revealed dilated intrahepatic bile ducts without pancreatic enlargement or evidence of liver metastasis. On the second hospital day, he developed a temperature of 39.6°C. Endoscopic retrograde cholangiopancreatography (Fig 2) revealed a common bile duct that was splayed and narrowed in multiple areas, consistent with extrinsic compression by enlarged lymph nodes. He was treated with cyclophosphamide, bleomycin, procarbazine hydrochloride, and prednisone, with complete resolution of jaundice, no further temperature elevations, and normalization of other liver function studies. He died in September 1985 of disseminated lymphoma without recurrence of jaundice.

COMMENT

Extrahepatic obstruction is an unusual feature of lymphoma. In one series of 370 patients, only 5 (1.3%) developed extrahepatic obstruction.[3] Both of our patients had clinical, biochemical, and roentgenographic evidence of cholestatic jaundice due to biliary obstruction. In both cases, CT or ultrasound revealed dilated bile ducts; however, the exact nature and site of obstruction were imprecise. In both cases,

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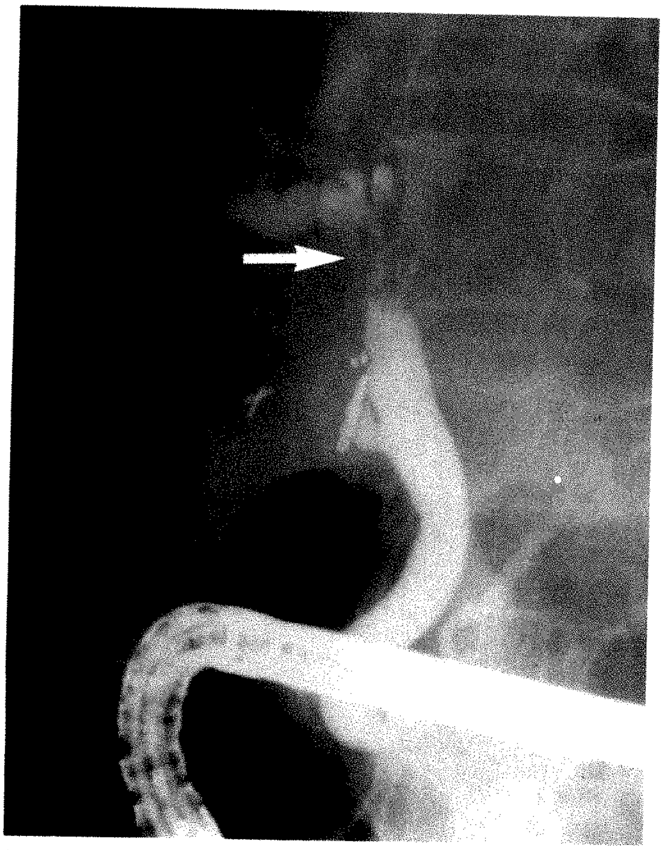

Fig 1.—Endoscopic retrograde cholangiopancreatography (case 1) shows an irregular stricture of the proximal common bile duct (arrow).

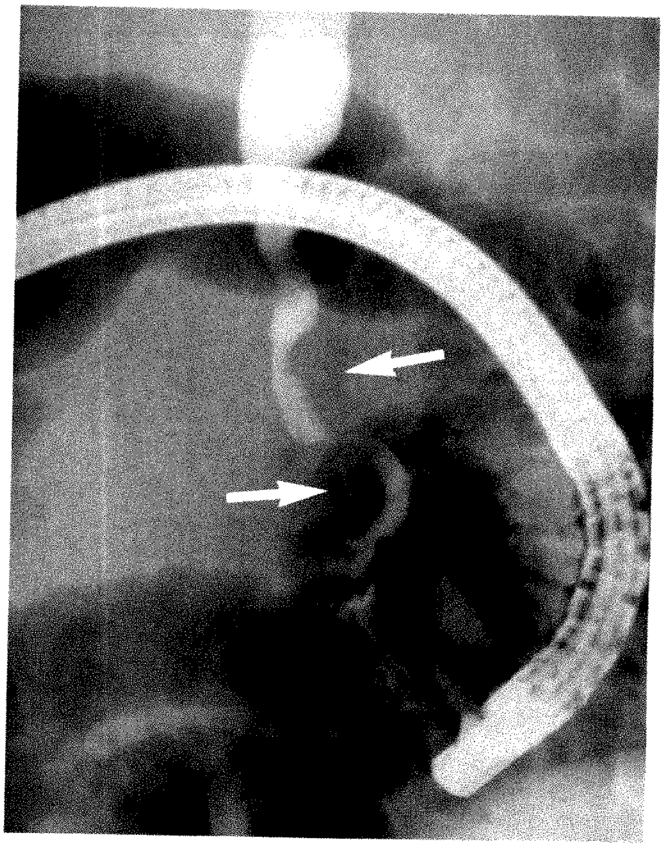

Fig 2.—Endoscopic retrograde cholangiopancreatography (case 2) shows a splayed common bile duct with multiple areas of narrowing (arrows) indicating extrinsic compression.

prior to ERCP, other diagnostic possibilities existed; these included biliary obstruction due to encroachment by a pancreatic malignancy encasing the intrapancreatic portion of the common bile duct, cholangiocarcinoma, sclerosing cholangitis, and, in case 2, benign obstruction due to a common duct stone. Endoscopic retrograde cholangiopancreatography delineated the site of obstruction and aided localization of the lesion for percutaneous biopsy in case 1 and demonstrated the nature of the obstruction in case 2.

Biliary involvement by lymphoma may occur by varied mechanisms. Primary histiocytic lymphoma of the pancreas involving the common bile duct by direct extension has been described.[6] Primary gastrointestinal lymphoma obstructing the bile duct at the ampulla of Vater has also been reported.[7] Intrinsic biliary obstruction by a diffuse lymphohistiocytic lymphoma arising in the bile duct has been documented to produce jaundice by direct growth, blocking the lumen of the duct.[8] However, most commonly lymphomatous nodes extrinsically compress the extrahepatic bile duct.[3,9,10]

The basic diagnostic modalities to assess biliary tract obstruction are ultrasound and CT. Either technique is excellent at detecting bile duct dilatation indicating obstruction, but neither is uniformly successful in delineating the site and nature of obstruction.[11] A problem in evaluating jaundice is that both ultrasound and CT can fail to detect minimal or localized duct dilatation. A further limiting factor is that the bile duct has a variable capacity for distensibility, and obstruction without dilatation of ducts can occur and be unidentified by imaging techniques.[12] In the lymphoma patient with unexplained jaundice and normal-sized bile ducts identified by CT or ultrasound, partial biliary tract obstruction must remain a diagnostic consideration. Accurate assessment by direct cholangiography may obviate the need for further evaluation, including percutaneous liver biopsy or laparotomy, in addition to preventing diagnostic error. Endoscopic retrograde cholangiopancreatography may also be useful for endoscopic biopsy of primary small-bowel lymphoma producing biliary obstruction by direct blockage of the ampulla of Vater. Placement of endoscopic stents bypassing the obstruction permanently or temporarily while treatment is instituted is also possible.[10] It may, however, be impossible at times to distinguish between extrinsic obstruction by large nodes or intrinsic obstruction by an intraductal tumor. In the patient having received prior radiotherapy to that area, the possibility of radiation-induced biliary stricture should also be considered.[13] Stenotic biliary disease due to *Cryptosporidium* or cytomegalovirus has recently been described in the acquired immunodeficiency syndrome and is a potential, though as yet unreported, complication in the patient who is immunosuppressed because of lymphoma.[14]

Extrahepatic biliary obstruction due to other malignancies, notably breast,[15] colon,[16] hepatoma,[17] and small-cell carcinoma of the lung,[18] has been reported as well. In certain cases, these tumors respond to specific chemotherapy, radiotherapy, or surgical bypass. Effective palliation may sometimes be achieved.[3,10,15] The sensitivity of some non-Hodgkin's lymphomas to radiation or chemotherapy suggests that recognition of obstruction may be of considerable clinical benefit in selected patients.

Patient 2 manifested an indolent non-Hodgkin's lymphoma based on the National Cancer Institute (NCI) clinical schema.[19] Treatment of such subsets with low-grade histologic features is a matter of some controversy. While long-term survival of most patients is the rule, many authors believe that there are no treatments for patients with any stage of indolent lymphoma that result in cure.[20] Patient 2 with stage I well-differentiated lymphocytic lymphoma (Rappaport classification) or small lymphocytic lymphoma (NCI Working Formulation) went into a complete remission with chemotherapy and radiation therapy, but recurrence of such a subtype was expected. When it did recur 3 years after presentation, a more aggressive chemotherapeutic approach was used. Five years later, a second recurrence, this time involving the common bile duct, was documented and once again an aggressive chemotherapeutic regimen was used. In this situation, the expectation of cure was small, although information is accumulating that supports the use of intensive combination chemotherapy for advanced stage, indolent lymphomas.[20]

The situation with more aggressive non-Hodgkin's lymphomas differs from that of the indolent non-Hodgkin's lymphomas since (seemingly paradoxically) there is the expectation of cure approximately one half of the time with intensive combination chemotherapeutic regimens.[20] In case 1, a diffuse, mixed, lymphocytic, histiocytic, stage IA lymphoma (Rappaport and NCI working formulation) was treated with single-agent chemotherapy initially, but rapidly developed more disseminated disease. Limited field radiation therapy produced regression of jaundice but disseminated disease developed and was refractory to chemotherapy. It might have been more appropriate to use a combination chemotherapy regimen early on, and many such are available and successful with low levels of toxic effects even in the elderly. Such regimens contain cyclophosphamide, doxorubicin, etoposide, methotrexate sodium, prednisone, mechlorethamine hydrochloride, vincristine, procarbazine (Pro-MACE-MOPP flexitherapy); or cyclophosphamide, doxorubicin, vincristine, bleomycin, methotrexate, dexamethasone therapy (m-BACOD); or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

The possibility of biliary obstruction should be considered in patients with lymphoma who also have jaundice or cholangitis. Similarly, biliary involvement by a lymphoma is a consideration in selected cases of unexplained cholestasis. The limited experience described herein suggests that ERCP is useful in demonstrating the site and nature of biliary obstruction in lymphoma; specific therapy may provide effective relief of jaundice and pruritus and reduce the risk of cholangitis. However, both our patients died within 7 months of developing extrahepatic obstruction, despite complete and continued resolution of jaundice. This poor prognosis is similar to the experience described by Boddie et al.[3] All five of their patients with this complication of lymphoma died within 6 months of onset of obstruction. Biliary obstruction may thus suggest a poor prognosis in non-Hodgkin's lymphoma.

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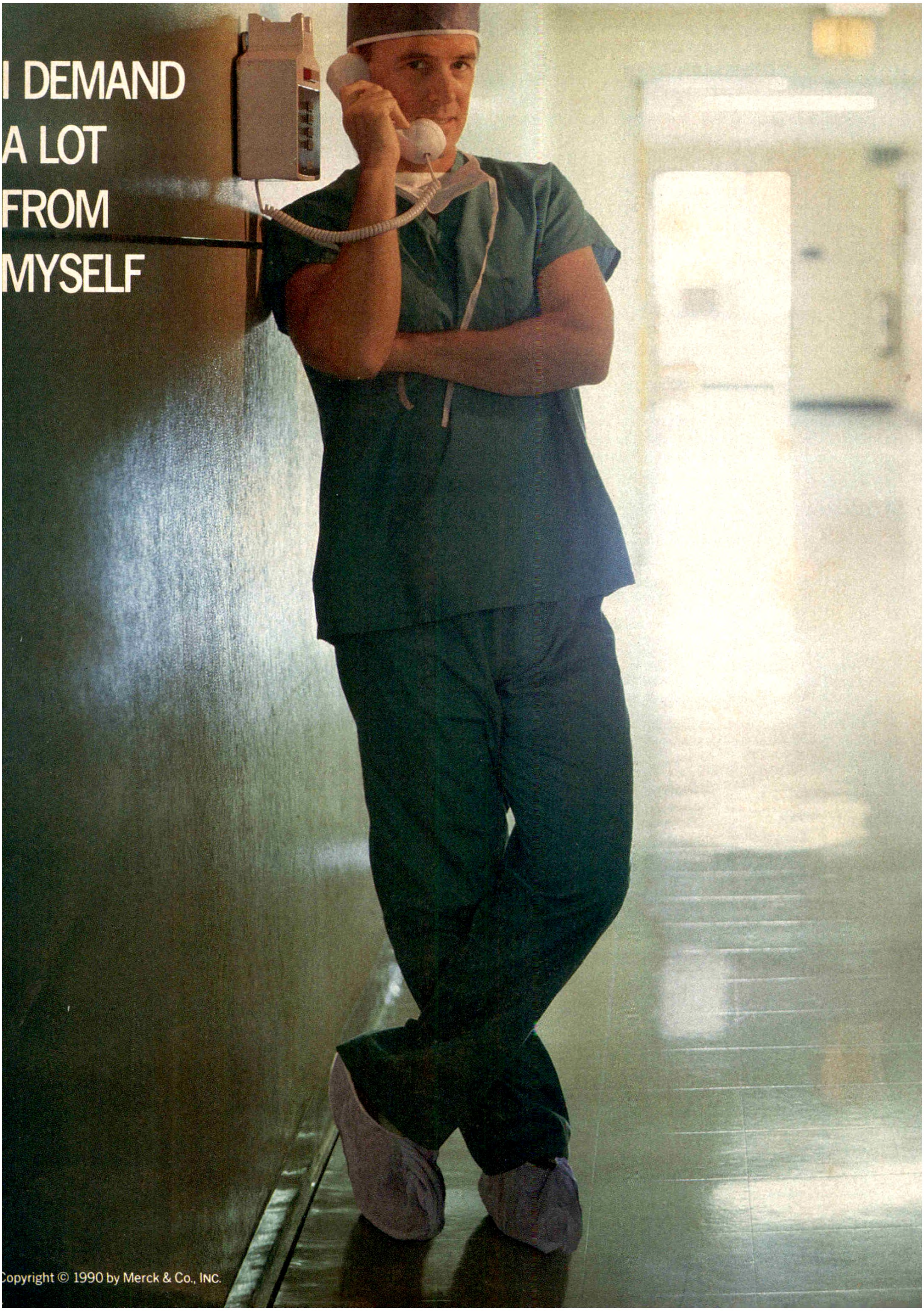

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ications and Usage: *Treatment*—Serious infections caused by susceptible strains of the designated
roorganisms in the following diseases:
VER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by *Strepto-*
cus pneumoniae, other streptococci (excluding enterococci, e.g., *Strep. faecalis*), *Staphylococcus aureus*
nicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Hemophilus influenzae*,
Bacteroides species.
NITOURINARY INFECTIONS. Urinary tract infections caused by *E. coli*, *Klebsiella* species, *Proteus*
abilis, indole-positive *Proteus* (which include the organisms now called *Morganella morganii* and *Proteus*
garis), and *Providencia* species (including *Providencia rettgeri*). Uncomplicated gonorrhea due to *Neis-*
a gonorrhoeae (penicillinase and non-penicillinase producing).
RA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli*,
siella species, *Bacteroides* species including the *B. fragilis* group,* and *Clostridium* species.
IECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease,
sed by *E. coli*, *N. gonorrhoeae* (penicillinase and non-penicillinase producing), *Bacteroides* species
uding the *B. fragilis* group,* *Clostridium* species, *Peptococcus* species. *Peptostreptococcus* species, and
up B streptococci.
TICEMIA caused by *Strep. pneumoniae*, *Staph. aureus* (penicillinase and non-penicillinase producing),
oli, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.*
IE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).
N AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase
ducing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*,
siella species, *Bacteroides* species including the *B. fragilis group*,* *Clostridium* species, *Peptococcus*
cies, and *Peptostreptococcus* species.
ough appropriate culture and susceptibility studies should be performed, therapy may be started while
iting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and
rococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylo-
ci are almost uniformly resistant to cefoxitin.
ention—Prophylactic use in surgical procedures (e.g., hysterectomy, gastrointestinal surgery, cesarean
ion, transurethral prostatectomy) classified as contaminated or potentially contaminated or in patients
hom subsequent infection at the operative site would present a serious risk, e.g., prosthetic arthroplasty.
OXIN usually should be given ½ to 1 hour before surgery and should usually be stopped within 24 hours
e continuing administration of any antibiotic increases the possibility of adverse reactions but, in the
ority of surgical procedures, does not reduce the incidence of subsequent infection. However, in patients
ergoing prosthetic arthroplasty, it is recommended that MEFOXIN be continued for 72 hours after the
gical procedure. If there are signs of infection, specimens for culture should be obtained for identification
e causative organism so appropriate treatment may be instituted.
traindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.
rnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE
VIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER
GS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINIS-
ED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICU-
LY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS
ERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.
udomembranous colitis, from mild to life-threatening in severity, has been reported with
ually all antibiotics (including cephalosporins); therefore, it is important to consider its
gnosis when diarrhea develops in association with antibiotic use. Broad-spectrum antibiotics
normal flora of colon and may permit overgrowth of clostridia; a toxin produced by *Clostridium difficile*
primary cause of antibiotic-associated colitis. Mild cases may respond to drug discontinuance alone; in
severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid,
trolyte and protein supplementation, and use of a drug such as oral vancomycin; isolation of the patient
may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—Total daily dose should be reduced in patients with reduced urinary output
renal insufficiency because high and prolonged serum antibiotic concentrations can occur from usual
Prescribe with caution in patients with a history of gastrointestinal disease, particularly colitis. Prol
use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condi
essential. If superinfection occurs, take appropriate measures.
Drug Interactions—Increased nephrotoxicity has been reported following concomitant administrat
cephalosporins and aminoglycoside antibiotics.
Drug/Laboratory Test Interactions—High concentrations (>100 mcg/mL) may interfere with measurem
serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest deg
creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2
of cefoxitin administration. High concentrations may interfere with measurement of urinary 17-hy
corticosteroids by the Porter-Silber reaction and produce false increases of modest degree in
reported. A false-positive reaction for glucose in urine has been observed with CLINITEST** reagent ta
Carcinogenesis, Mutagenesis, Fertility Impairment—No long-term animal study has been perform
carcinogenic or mutagenic potential. Rat studies at approximately three times maximum recomm
human dosage revealed no effects on fertility or mating ability.
Pregnancy Category B—Reproduction studies in rats and mice did not reveal teratogenic or fetal
effects, although fetal weights were slightly decreased. In rabbits, cefoxitin was associated with a
incidence of abortion and maternal death, neither considered teratogenic. There are, however, no ade
and well-controlled studies in pregnant women. Because animal reproduction studies are not a
predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers—Excreted in human milk: Exercise caution.
Pediatric Use—Safety and efficacy in infants from birth to three months have not yet been establish
children three months and older, higher doses have been associated with increased incidence of eosino
and elevated SGOT.
Adverse Reactions: The most common adverse reactions have been local reactions following intrave
or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reacti*
Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramus
injections. *Allergic Reactions*—Rash (including exfoliative dermatitis), pruritus, eosinophilia, fever, and
allergic reactions including anaphylaxis. *Cardiovascular*—Hypotension. *Gastrointestinal*—Diarrhea, in
ing documented pseudomembranous colitis during or after treatment, and, rarely, nausea and vom
Blood—Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hem
anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may devel
some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, s
LDH, and serum alkaline phosphatase; jaundice. *Renal Function*—Elevations in serum creatinine a
blood urea nitrogen levels and, rarely, acute renal failure.
Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10
to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infec
involving a collection of pus, surgical drainage should be carried out where indicated. Intramus
injections should be well within the body of a relatively large muscle such as the upper outer quadrant c
buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel
total daily dosage in infants and children should not exceed 12 grams.
How Supplied: Sterile cefoxitin sodium in vials, infusion bottles, and ADD-Vantage®† vials conta
1 gram or 2 grams cefoxitin equivalent and in 10-gram bulk bottles.

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gilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus

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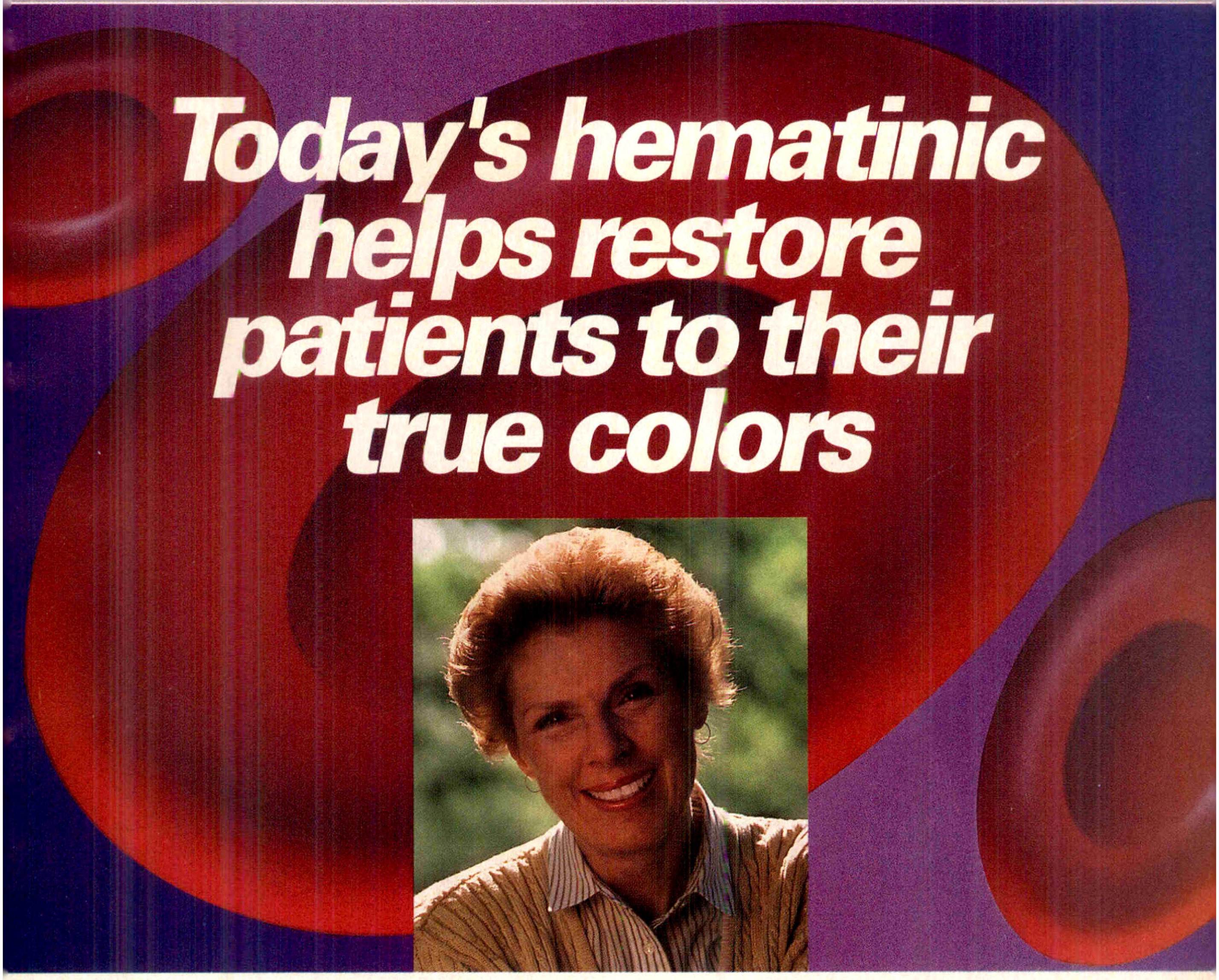

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Brief Summary
TRINSICON®

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Russ Pharmaceuticals, Birmingham, AL 35242
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June 1990

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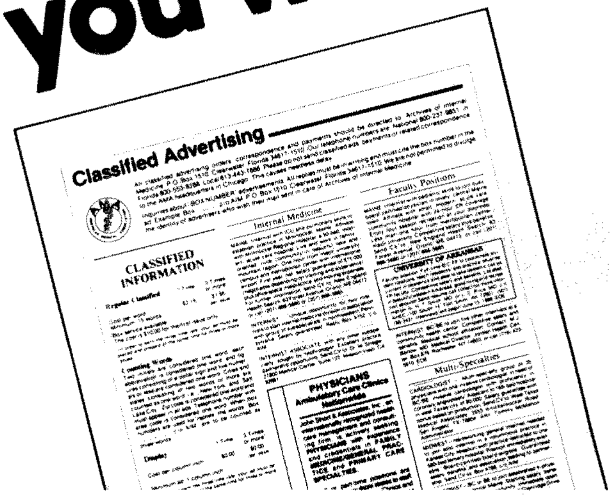

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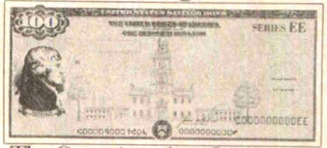

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Books

Lung Cancer Chronicles, by John A. Meyer, 233 pp, with illus, $35 (cloth), $10 (paper), New Brunswick, NJ, Rutgers University Press, 1990.

John A. Meyer, PhD, has written an up-to-date and informative book about lung cancer intended for the layman. The book is a combination of case histories, science, opinions, epidemiology, and the fictional physician Bill Hunter. While it contains fictional characters, the book is not a novel; it has no plot, beginning, or end. Treatment modalities presented in the text follow epidemiologic data, and clinical relationships are presented through the interspersing of anecdotal cases from the beginning of the book.

In his book, Meyer places great emphasis on the hazards of smoking. He points out that most lung cancers are preventable, preferably by never smoking rather than by stopping once one has started, although the latter is beneficial. He mentions the financial and political aspects of growing tobacco and summarizes in chapter 16, perhaps too briefly, some of the court cases relating to product liability and the tobacco industry.

The statistical explanations throughout the text are often oversimplified. Some discussions of principles seem convoluted. The book is referenced like a medical journal article. The appendixes and glossary are useful but are more suggestive of beginning science than anything else.

As a minor criticism, I take issue with the evaluation of some of Meyer's fictional patients. Mediastinoscopy is carried out far too often, even in one situation where there is already widespread metastatic disease. Magnetic resonance imaging gets nary a mention.

This book contains a good deal of pertinent information. Patients with lung cancer or their families might find the book useful. As Meyer correctly points out, however, "Its words should not ever be relied upon above or in place of the advice of a personal physician." The book seems very appropriate for a high school student looking for source material for a report on lung cancer, and a wider lay audience will appreciate it. It is too elementary for thoracic surgeons or pulmonologists, but other physicians who treat patients with lung cancer may find it useful.

JAMES B. D. MARK, MD
Stanford, Calif

Correspondence and Brief Communications

Intestinal Fistulas and the Open Management of the Septic Abdomen

To the Editor.—In the June 1989 issue of the ARCHIVES, Mastboom et al[1] described what they call "noniatrogenic" small-bowel perforations of "unknown or uncertain" cause, which developed in 14 patients treated by open treatment who underwent 3 to 17 laparotomies, and claim that the "occurrence of intestinal perforation during open treatment has not been described so far."

In fact, the article by Mastboom et al deals with a well-known and documented entity. Intestinal fistulas commonly develop in the frequently laparotomized abdomen due to the repeated mobilization and separation of bowel involved in the obliterative process. Commonly, the end result of repeated explorations is an abdominal-wall defect with multiple intestinal fistulas in its base. Sitges-Serra et al[2] pointed out the poor prognosis of this entity, which in their experience carried a mortality rate of 60%. Levy et al[3] reported 120 cases of "exposed" intestinal fistulas opening into an abdominal evisceration, including 24 "wall-to-bowel" fistulas secondary to external trauma on a superficial intestinal loop. Similarly, "spontaneous" intestinal perforations are dreaded complications of open treatment.[4] The introduction of a polypropylene mesh (Marlex mesh) in open treatment, as used by Mastboom and associates, has minimized the risk of fistulization. However, fistulization does occur, particularly when there is delay in mesh removal and skin grafting.[5] Recently, we reported our experience with 43 cases of gastrointestinal fistulas associated with a large abdominal-wall defect; in 19 cases, this defect was created intentionally by open treatment.[6] Intestinal leaks occur, in such a set-up, as a result of exposure injury, dehiscence of preexisting suture lines (even after many days), and trauma of abdominal reentry.

I must also disagree with the therapeutic recommendations suggested by Mastboom et al, who claimed that resection of the intestinal defects with primary anastomosis resulted in the "success" of 18% recurrences, followed by an overall mortality rate of 65%. I believe that the distance of the fistulous opening in the bowel from the surface of the abdominal-wall defect and the condition of the peritoneal cavity have bearing on the treatment modalities. When the intestinal perforation is located in the depth of the infected abdominal defect, the prolonged contact of large peritoneal surfaces with gastrointestinal contents allows increased absorption of toxic products perpetuating the septic state and organ failure. In such a situation, in my experience, the only surgical option to salvage the patient is a prompt diversion of the intestinal leak away from the defect, with a proximal enterostomy. In patients who present, usually later, with "exposed fistulas" near the surface of the defect and in whom the peritoneal cavity is clean and sealed away from the intestinal contents, the expectant approach is indicated. Early resection and the creation of anastomoses (as suggested by Mastboom et al), leaving the suture-line exposed or under the skin grafts, carries disastrous results. Consequently, my approach is to leave these patients "untouched" for at least 6 months receiving total parenteral nutrition. Reestablishment of gastrointestinal continuity is undertaken in an anabolic patient through a healed and pliable abdominal wall; easy and safe resection and anastomoses of the fistulating bowel are performed after the dissolution of the peritoneal obliterative process. In addition, the bowel remains well covered by the abdominal wall, which is reconstructed at the same time.

MOSHE SCHEIN, MD, FCS(SA)
Johannesburg, South Africa

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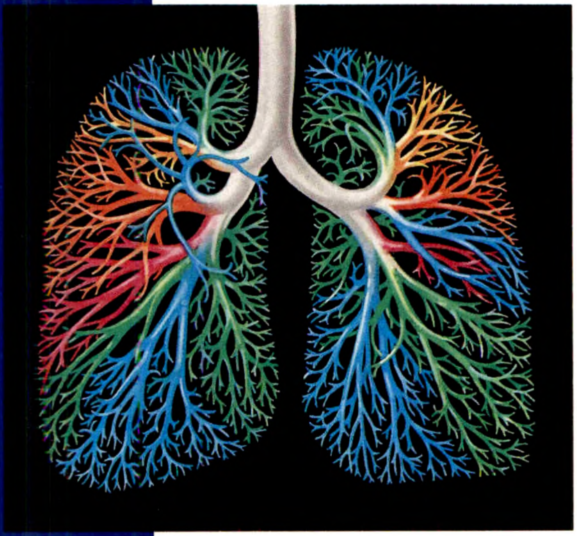
THE RESPIRATORY SEASON MEANS



TOUGH PATIENTS, TOUGH PATHOGENS...

* Achieves 96% favorable clinical response (resolution + improvement) of infections due to susceptible strains of indicated pathogens. See indicated organisms in prescribing information.

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Antacids containing magnesium hydroxide or aluminum hydroxide interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

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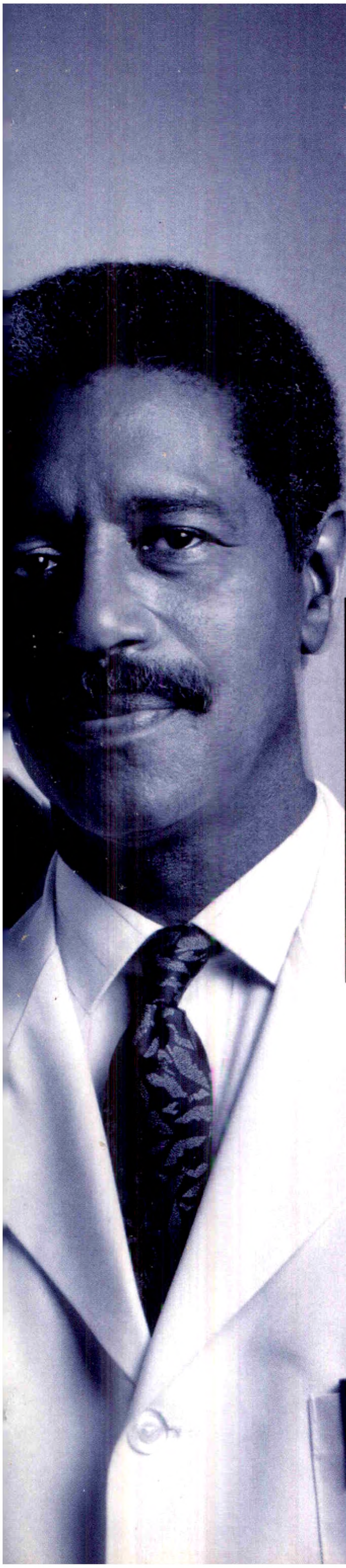
See last page for brief summary of prescribing information.



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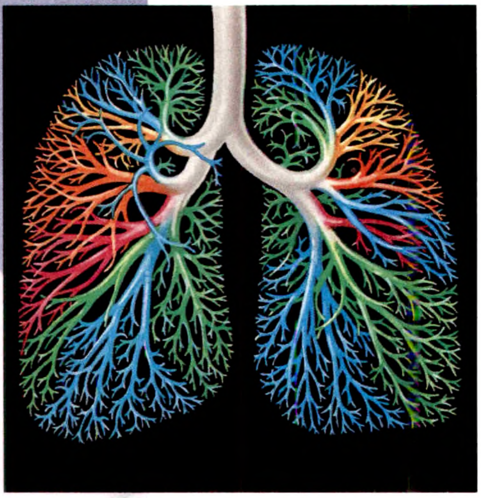

Treating patients with lower respiratory infections is often a challenge.

These patients may smoke or drink excessively, or have underlying conditions such as COPD.

They could be elderly or immunocompromised or live in nursing homes where they are constantly exposed to multiple organisms.

Too often, they may have a history of repeated antibiotic use that has proven ineffective against their lower respiratory infections.

So, how do you manage these tough patients during the respiratory season?

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Cipro® TABLETS

(ciprofloxacin HCl/Miles)

The most potent fluoroquinolone.[2-4†]

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IN LOWER RESPIRATORY INFECTIONS

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BRIEF SUMMARY
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INDICATIONS AND USAGE

Cipro® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Lower Respiratory Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*.

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*,* and *Shigella sonnei** when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Anaphylactic reactions following the first dose have been reported in patients receiving therapy with quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reaction. Anaphylactic reactions may require epinephrine and other emergency measures. Ciprofloxacin should be discontinued at the first sign of hypersensitivity or allergy.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have been reported rarely (less than one per million prescriptions) in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any sign of other hypersensitivity reaction.

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION). Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded.

Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION).

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Drug Interactions: As with other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with a quinolone has been reported to increase the risk of CNS stimulation and convulsive seizures.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum.

Patients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight in vitro mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Patients under the age of 18 were not included in the clinical trials of ciprofloxacin because ciprofloxacin as well as other quinolones causes arthropathy in immature animals. Ciprofloxacin should not be used in children or adolescents (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%). Those events typical of quinolones are italicized.

The most frequently reported events, drug related or not, were *nausea* (5.2%), *diarrhea* (2.3%), *vomiting* (2.0%), *abdominal pain/discomfort* (1.7%), *headache* (1.2%), *restlessness* (1.1%), and *rash* (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below.

GASTROINTESTINAL: *(See above)*, painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: *(See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.*

SKIN/HYPERSENSITIVITY: *(See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands*, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported (SEE PRECAUTIONS).

SPECIAL SENSES: *blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste.*

MUSCULOSKELETAL: *joint or back pain, joint stiffness*, achiness, neck or chest pain, flare-up of gout.

RENAL/UROGENITAL: *interstitial nephritis, nephritis, renal failure*, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Other adverse events reported in the postmarketing phase include anaphylactoid reactions, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hepatic necrosis, postural hypotension, possible exacerbation of myasthenia gravis, confusion, dysphasia, nystagmus, pseudomembranous colitis, dyspepsia, flatulence, and constipation. Also reported were agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria, vaginal candidiasis; and renal calculi (SEE PRECAUTIONS).

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic—Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Cholestatic jaundice has been reported.

Hematologic—Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal—Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Lower respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro® (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE DESCRIPTION).

References: 1. Data on file, Miles Inc Pharmaceutical Division. **2.** Barry AL, Jones RN, Thornsberry C, et al. Antibacterial activities of ciprofloxacin, norfloxacin, oxolinic acid, cinoxacin, and nalidixic acid. *Antimicrob Agents Chemother.* 1984;25:633-637. **3.** Guimaraes MA, Noone P. The comparative *in-vitro* activity of norfloxacin, ciprofloxacin, enoxacin and nalidixic acid against 423 strains of gram-negative rods and staphylococci isolated from infected hospitalised patients. *J Antimicrob Chemother.* 1986;17:63-67. **4.** Van Caekenberghe DL, Pattyn SR. In vitro activity of ciprofloxacin compared with those of other new fluorinated piperazinyl-substituted quinolone derivatives. *Antimicrob Agents Chemother.* 1984;25:518-521.

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In Reply.—Dr Schein disagrees with our supposition that the occurrence of nontraumatic small-bowel perforations during open treatment for intra-abdominal sepsis has not been described so far and states that it is a well-known and documented entity.

Intestinal perforations and fistulizations are indeed common complications in patients treated for intra-abdominal sepsis, but there are obvious causes for fistulization in all cases reported in the literature, such as abdominal reentry damage, anastomotic breakdown, or abdominal-wall dehiscence.

Dr Schein cites several references to support his argument but, again, all these cases had obvious causes. The article by Sitges-Serra et al deals with 87 fistulas, all secondary to either anastomotic breakdown, direct trauma to the small bowel, or small-bowel inflammation. In the article by Levy et al, causes for fistulization were anastomotic dehiscence (52%), small-bowel trauma (41%), abdominal-wall necrosis (1.7%), and a combination of these factors (5.3%). Schein's own group[1] described a patient with a small-bowel fistula that, as they stated, was due to the polypropylene mesh. Bradley and Fulenwider[2] reported a similar experience.

The perforations described by us developed in the granulating layers of left-open abdomens, not in abdominal-wall dehiscences. They occurred in intact segments of the small bowel, not in preexisting suture lines, and they were not the result of reentry damage, because then they would have been treated either by suturing (and sutures would have been present at the site of perforation) or by creating a stoma. Therefore, they were not the result of well-known causes but indeed formed an entity that has not been described previously.

When not treated, the perforations became large defects in granulating layers, mimicking loop enterostomies, that could not be dealt with adequately. An expectant approach, as in small enterocutaneous fistulas (which Dr Schein probably thinks we are dealing with), was not possible. There were no recurrences after resection and primary anastomosis, but the recurrence rate was 18% after closing in layers. Finally, the mortality in this series (64%) was not related to the occurrence of perforations but to the underlying disease. Therefore, we stick to our therapeutic recommendations.

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THEO WOBBES, MD, PHD
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Elective Cholecystectomy After Biliary Lithotripsy: An Indication for Routine Intraoperative Cholangiography?

To the Editor.—Given the increasing popularity of extracorporeal shock wave biliary lithotripsy and the fact that small stone fragments leave the gallbladder via the common bile duct, the complications of this therapy are now becoming more apparent. We report a case of a patient who underwent elective cholecystectomy after failing biliary lithotripsy. There were no indications of intraoperative cholangiography except the presumption that stone fragments were likely to have traveled down the common bile duct.

Report of a Case.—A 50-year-old Hispanic woman presented with recurrent postprandial right upper quadrant pain and nausea 6 months after undergoing biliary lithotripsy for symptomatic cholelithiasis. These symptoms began 10 years before admission. Prior to lithotripsy, a single 2-cm gallstone was documented sonographically. Her symptoms persisted and she requested surgical treatment. She denied a history of dark urine, acholic stools, jaundice, fever, or chills. Physical examination was significant for a well-appearing anicteric woman without abdominal tenderness or palpable masses. Complete blood cell counts and results of liver function chemistry analyses were normal. A repeated sonogram demonstrated multiple gallstones and normal gallbladder wall thickness. The common bile and intrahepatic ducts were not dilated and there were no stones seen within the common bile duct.

At operation, the gallbladder was found to be noninflamed and multiple gallstones were palpable. The common bile duct was of normal caliber. A routine cholecystectomy was performed, and an intraoperative cystic duct cholangiogram revealed three small filling defects in the distal common bile duct. A common bile duct exploration was performed in the usual fashion with the retrieval of three small angulated cholesterol stones, each measuring less than 1 cm. A follow-up T-tube cholangiogram revealed no residual filling defects and prompt flow of contrast material into the duodenum.

Comment.—With the above considerations in mind, we feel that the list of indications for routine cystic duct cholangiography should be expanded to include those patients who undergo elective cholecystectomy following attempted biliary lithotripsy.

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10. Extent and Nature of Circulation *(See instructions on reverse side)*	Average No. Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
A. Total No. Copies *(Net Press Run)*	10/89-09/90 54,052	09/90 40,591
B. Paid and/or Requested Circulation 1. Sales through dealers and carriers, street vendors and counter sales	642	653
2. Mail Subscription *(Paid and/or requested)*	51,290	38,208
C. Total Paid and/or Requested Circulation *(Sum or 10B1 and 10B2)*	51,932	38,861
D. Free Distribution by Mail, Carrier or Other Means Samples, Complimentary, and Other Free Copies	-0-	-0-
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2. Return from News Agents	-0-	-0-
G. TOTAL *(Sum of E, F1 and 2—should equal net press run shown in A)*	54,052	40,591

11. **I certify that the statements made by me above are correct and complete**

Signature and Title of Editor, Publisher, Business Manager, or Owner

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PS Form **3526**, Feb. 1989

(See instructions on reverse)

Instructions for Authors

Manuscripts are to be sent by first-class mail to the Editor, Claude H. Organ, Jr, MD, Professor, Dept of Surgery, University of California–Davis, East Bay 1411 E 31st St, Oakland, CA 94602. The procedures listed must be followed carefully and all materials requested must be enclosed for prompt review and consideration for publication in the *Archives of Surgery.* Use the checklist to ensure completeness.

Manuscript Preparation.—*The original typescript and two high-quality copies* of the entire manuscript must be submitted, including copies of all illustrations, legends, tables, and references. All copy, including references, legends, and tables, must be typed double-spaced on 8½ × 11-in, heavy-duty white bond paper. Margins must be at least 1 in. If a word processor is used, do *not* use justified right margins.

Abstract.—*Submit an abstract* (135-word maximum) of the manuscript, which must include a statement of the problem, methods of study, results, and conclusions. The synopsis-abstract replaces a summary or conclusions.

Copyright.—*A copyright release* form signed by *all* authors of manuscripts, brief communications, and correspondence is required by the Copyright Revision Act of 1976. The following statement, dated and signed by all authors, may be used: **"In consideration of the American Medical Association's taking action in reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to the AMA in the event that such work is published by the AMA."**

Financial Interest.—List all affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials of the research discussed in the manuscript (eg, employment, consultancies, stock ownership). All such information will be held in confidence during the review process. Should the manuscript be accepted, the Editor will discuss with the author the extent of disclosure appropriate for publication.

References.—*References* should be listed in *consecutive numerical order* as they are cited in the text, *not alphabetically.* Once a reference is cited, all subsequent citations should be to the original number. All references must be cited in the text or tables. Unpublished data and personal communication may not be listed as references. References to journal articles should include (1) authors (list all authors and/or editors up to six; if more than six, list the first three and "et al"), (2) title, (3) journal name as abbreviated in *Index Medicus,* (4) year, (5) volume number, and (6) inclusive page numbers—in that order. References to books should include (1) authors (list all authors and/or editors up to six; if more than six, list the first three and "et al"), (2) chapter title, if any, (3) editor, if any, (4) title of book, (5) year, (6) city, and (7) publisher. Volume and edition numbers, specific pages, and name of translator should be included when appropriate. **The author is responsible for the accuracy and completeness of the references and for their correct text citation.**

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- Three copies of synopsis-abstract.
- Three copies of attached photographs, legends, tables, and/or illustrations clearly marked as described in the instructions.
- A copyright release statement signed by *all* authors.
- The address and telephone number of the designated corresponding author.
- Send to Claude H. Organ, Jr, MD
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  Professor, Dept of Surgery
  University of California–Davis, East Bay
  1411 E 31st St
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- Use sufficient postage.

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OTHER INFORMATION

Brief Clinical Notes.—The ARCHIVES welcomes the submission of Brief Clinical Notes for review. These are generally reports of cases that provide a new or unique contribution and are to consist of no more than 400 words, two references, and one illustration. The synopsis-abstract may not exceed 80 words.

Correspondence and Brief Communications.—The Editor is pleased to receive letters that pertain to material published in the ARCHIVES as well as brief communications concerning other matters of interest to our readers. An interesting case may be published as a brief communication. Such contributions should be 250 words or less, typewritten, double-spaced without an abstract, and clearly marked "for publication." No more than two references are permitted and illustrations or tables are acceptable only when essential to the message.

News and Announcements.—Brief notices may be submitted of meetings, seminars, or symposiums that are of interest to surgeons.

Acknowledgments.—Illustrations from other publications must be acknowledged. Include the following when applicable: authors, title of article, title of journal or book, volume number, pages, month and year. The publisher's permission to reprint must be submitted to the ARCHIVES when the manuscript has been formally accepted.

Statistical Review.—Manuscripts containing statistical evaluation should include the name and affiliation of the statistical reviewer.

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Reference to Patients.—Patients should be referred to by number or, in anecdotal reports, by fictitious given names. Real names or initials must not be used in the text, tables, or illustrations.

Photographic Consents.—A letter of consent must accompany all photographs of patients in which a possibility of identification exists. It is *not* sufficient to simply cover the eyes to mask identity.

AMA Manual of Style.—This 1988 edition, formerly the *Manual for Authors & Editors*, is available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202. Single copy price: $26.95. A shipping charge is added on all orders not prepaid. If additional ordering information is needed, or to order by telephone, call 1-800-638-0672.

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All classified advertising orders, correspondence and payments should be directed to: Archives of Surgery, P.O. Box 1510, Clearwater, Florida 34617. Our telephone numbers are: 800-237-9851; 813-443-7666. Please do not send classified ads, payments or related correspondence to the AMA headquarters in Chicago. This causes needless delay.

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DEPARTMENT OF VETERANS AFFAIRS Medical Center, Tuskegee, Alabama 36083, has a vacancy for a pulmonologist. Must be a citizen or possess permanent immigrant visa. Must be board-certified or -eligible. Excellent weather. Salary ranges from $75,000 to $91,000 dependent upon qualifications and experience. An equal opportunity employer – F/H/M. Contact: Chief of Staff (205) 727-0550, Extension 3645.

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Multi-specialty group in suburban Philadelphia needs a BE/BC oncologic surgeon for clinical practice. Preference given to candidates with thoracic and vascular expertise. Endoscopic skills also desired. Excellent benefits and salary leading to full partnership position. Send curriculum vitae and references to:

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IMMEDIATE OPENING for board-eligible or -certified surgeon, preferably with endoscopy experience, at progressive VA medical center located in Michigan's upper peninsula. This well-equipped, 200-bed general medical and surgical center offers competitive salary and benefits. The community offers ideal family living in town of 18,000 people with good schools, low cost of living, short commuting distance, and year-round recreational activities. Applicants should reply to: Chief of Staff, VA Medical Center, Iron Mountain, MI 49801. Equal opportunity employer.

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Are you looking for challenging and outstanding opportunities for professional growth? Do you value a good school system, low crime rate, clean air and unsurpassed scenic beauty? Then St. Mary's Hospital in Pierre, South Dakota is what you are looking for.

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WANTED: BE/BC general surgeon with interest and experience in non-cardiac thoracic surgery, or thoracic surgeon who enjoys general surgery, to assume practice of retiring double boarded thoracic/general surgeon. 34 member, multi-specialty group in dynamic area hub city of 35,000, with six satellite offices in strategic locations, and referral area of 300,000 plus. Superb hospital facilities, including CT, MRI, cardiac surgery neurosurgery, etc. Directed toward those concerned about quality family lifestyle and professional concerns. Contact: Recruitment Coordinator, Park Clinic, 890 North Eisenhower Avenue, Mason City, IA 50401. Or dial: (800) 798-4321 for more information

COLO-RECTAL SURGEON — Multi-specialty group in suburban Philadelphia needs a BE/BC colo-rectal surgeon for clinical practice. Excellent benefits and salary leading to full partnership position. Send curriculum vitae and references to: Surgical Services, Ltd., Moss Plaza, Suite 206, 9892 Bustleton Avenue, Philadelphia, PA 19115. Attention: Robin Eric Rosenberg, MD.

LOVINGTON, NEW MEXICO: General surgeon needed for solo practice under the warm sun of southeastern New Mexico; assistance with start-up costs is available. Excellent practice potential in this peaceful, family-oriented community, close to world-renowned Carlsbad Caverns. Contact: NM Health Resources, Box 27650, Albuquerque, NM 87125. (505) 260-0993. Not-for-profit, no-fee placement.

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OUTSTANDING, board-certified, general surgery opportunity in beautiful Ozark region of southwestern Missouri. Enjoy one in three call/coverage with immediate referrals from five family practice physicians. Beautiful, modern, 60-bed hospital is only nine years old. Community has excellent schools, university, and numerous lakes within fifteen miles. Located only 28 miles from Springfield, the third largest city in Missouri. Tremendous financial package includes minimum $125,000 net guarantee with no pay back, paid malpractice insurance, benefits, and relocation expenses. Send CV or call: Todd Dillon, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 AS0, Atlanta GA 30346. Telephone (800) 544-1987.

GENERAL SURGERY — Opportunity to live and work in the beautiful state of Hawaii. Established in 1903, The Honolulu Medical Group is seeking a BC/BE general surgeon to join our 45-physician multi-specialty group. We offer the opportunity to retain control of the medical directive while eliminating the headaches of administration and recruiting. Plus an attractive salary/benefits package and an excellent working environment. Send CV to: Chairman, Physician Recruitment, The Honolulu Medical Group, 550 South Beretania Street, Honolulu, HI 96813. Or FAX to: (808) 531-4179. Equal opportunity employer.

VASCULAR SURGEON with fellowship training to join well-established group of cardiothoracic surgeons and a vascular surgeon. Opportunity is located in suburb of Indianapolis with access to major universities, cultural amenities, and many recreational activities. Office space is tastefully decorated and is adjacent to 460-bed hospital. Great rapport among the physicians, and the support staff is excellent. Guaranteed salary, full benefits package, and interviewing and relocation expenses offered. Send CV or call: Patty Martens, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 AS0, Atlanta, GA 30346. Telephone: (800) 544-1987.

MENDOCINO COUNTY — Immediate opening in beautiful coastal northern California fo full-time BC/BE general/vascular surgeon with trauma experience. Send CV to: Julie Campbell, Mendocino Coast District Hospital, 700 River Drive, Fort Bragg, CA 95437. Or call: (707) 961-1234.

Professional Opportunities

GENERAL SURGEON — Olmsted Medical Group is experiencing continuous growth and currently seeking a BC/BE general surgeon to join a busy, two-physician department. Excellent opportunity for a well-trained physician to join a 50 plus physician multi-specialty group in a dynamic, progressive practice. Affiliate hospital recently underwent complete renovation/expansion. Competitive salary/comprehensive benefit package: malpractice insurance, flexible benefits plan, 401K and profit sharing, relocation assistance. Send CV: Olmsted Medical Group, Attention: Susan Schuett, 210 Ninth Street Southeast, Rochester, MN 55904.

GENERAL/VASCULAR SURGEON—BC/BE with recent training to join established two-person practice in southeastern Massachusetts. Interest in vascular surgery required. Busy practice is based at 275-bed community teaching hospital located 25 miles from Boston. Send CV or call: Kelly McMahon, Daniel Stern and Associates, 211 North Whitfield Street, Suite 240, Pittsburgh, PA 15206. (800) 438-2476.

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CARDIOVASCULAR AND THORACIC SURGEON wanted to join a busy, expanding practice in the western suburbs of Chicago. Excellent opportunity for BC/BE, university trained individual. Please forward CV with letter of introduction to: Box #917, c/o AOS.

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Contact:
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GARRETT SURGICAL GROUP
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(301) 334-8282

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Chief of Staff

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Director, Trauma Services
Department of Surgery
St. Louis University Medical Center
P.O. Box 15250
St. Louis, MO 63110-0250
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Dr. H.M. Lee, Department of Surgery
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Surgery Boards Review Course

November 2-4 – Baltimore December 7-9 – Miami
February 22-24 – New Orleans† April 26-28 – Omaha†

Now, a special update for your written, recertification, or oral exam

OBJECTIVES

- To increase knowledge of surgical principles and practice
- To prepare candidates to take written and oral board exams
- To provide a comprehensive review for recertification

METHODS

- HOME STUDY questions, assignments and answers
- SEMINAR with projection slides and syllabus
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*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

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November 2-4 – Baltimore
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April 26-28, 1991 – Omaha †
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Sept. 20-22 – Pittsburgh †

The Part II Course is to prepare board candidates for oral exams through mock oral exams on differential diagnosis, treatment options, and complications. Faculty will critique exams and answer questions.

Each participant will have an exam and unlimited observation of other sessions. Additional 25 minute sessions may be arranged for $70 and private sessions may be arranged for an additional $30. Mock oral sessions will include diseases and trauma of:

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Alimentary Tract
Breast Surgery
Thoracic Surgery
Head and Neck Surgery
Vascular Surgery
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General Surgery

Alimentary Tract
Abdominal Surgery
Breast and Skin
Endocrine Surgery
Head and Neck

Special Surgery

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- **Add 10% within 10 days of the course.**
- Attendees not in course hotel add $20/day.
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The University of Texas Health Science Center at Houston, Division of Continuing Education, designates this continuing medical education activity, November 2-4, for **28 credit hours** (Part II Course) **in Category 1** of the Physician's Recognition Award of the American Medical Association.

*"...home study material was extremely helpful."**

REFUNDS: Subject to a $50 fee, refunds will be made up until the seminar begins.

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INFORMATION:

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The Osler Institute
1094 Dawn Lane, P.O. Box 2218
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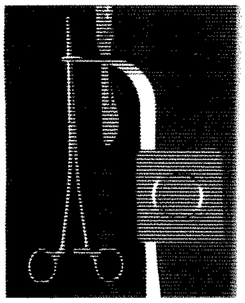
(800) 356-7537 or (812) 299-5658

**Comments by participants.*
†Course being planned, awaiting C.M.E.



Count on

CEFOTAN® IM/IV (cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri,* and *Morganella morganii*).
Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*
Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli.*
Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).
Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus.**
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.
NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.
INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.
DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.
USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.
PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.
IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:} \quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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Rev. I 11/88

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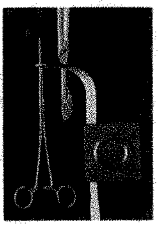
Cefotan arithmetic.

+ more cost-effective than cefoxitin[1,2]

− less frequent dosing than cefoxitin[3,4]

× several times the half-life of cefoxitin[5,6]

÷ single-dose prophylaxis/ twice-daily treatment



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(cefotetan disodium)
In intra-abdominal and gynecologic infection due to indicated organisms

References: 1. Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. 2. Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. 3. CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. 4. *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. 5. Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. 6. Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

Please see adjacent page for brief summary of prescribing information.

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December 1990
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UCM

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COMMENTARY

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Condon

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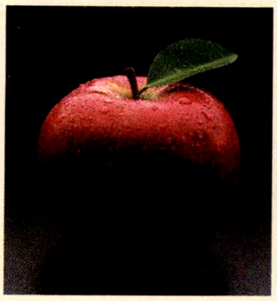
Once for prophylaxis. Once daily for cure.

The prophylactic dose of ROCEPHIN is also the daily therapeutic dose. ROCEPHIN, 1 gm given once prior to surgery,* provides effective prophylaxis against infection and is on board throughout the perioperative period—even if surgery is delayed or prolonged.

And ROCEPHIN, 1 gm given once a day, is the therapeutic dosage for the following common postsurgical infections: respiratory tract or skin/skin structure infections due to *Staphylococcus aureus, Klebsiella pneumoniae* and *Proteus mirabilis;* urinary tract infections due to *Escherichia coli, K. pneumoniae* and *P. mirabilis.*

Efficacy, economy and ease. ROCEPHIN 1 gm once for prophylaxis, once daily for cure.



Once-a-day

Rocephin® IV·IM

ceftriaxone sodium/Roche

As with any cephalosporin, there exists the possibility of hypersensitivity reactions, especially in individuals with a history of sensitivity.

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Please see adjacent page for summary of product information.

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* In contaminated or potentially contaminated procedures (*e.g.,* vaginal or abdominal hysterectomy), and for patients in whom infection at the operative site would present serious risk (*e.g.,* coronary artery bypass graft [CABG] surgery).

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep. pneumoniae, Streptococcus* species (excluding enterococci), *Staph. aureus, H. influenzae, H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *E. coli, E. aerogenes, Proteus mirabilis* and *Serratia marcescens*.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus, Staph. epidermidis, Streptococcus* species (excluding enterococci), *E. cloacae, Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*.

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli, Proteus mirabilis, Proteus vulgaris, M. morganii* and *Klebsiella* species (including *K. pneumoniae*).

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains.

PELVIC INFLAMMATORY DISEASE caused by *N. gonorrhoeae*.

BACTERIAL SEPTICEMIA caused by *Staph. aureus, Strep. pneumoniae, E. coli, H. influenzae* and *K. pneumoniae*.

BONE AND JOINT INFECTIONS caused by *Staph. aureus, Strep. pneumoniae, Streptococcus* species (excluding enterococci), *E. coli, P. mirabilis, K. pneumoniae* and *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS caused by *E. coli* and *K. pneumoniae*.

MENINGITIS caused by *H. influenzae, N. meningitidis* and *Strep. pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph. epidermidis* and *E. coli*.

SURGICAL PROPHYLAXIS: Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (*e.g.*, vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (*e.g.*, during coronary artery bypass surgery).

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery. When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure.

SUSCEPTIBILITY TESTING: Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and/or determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, reported with nearly all antibacterial agents, including ceftriaxone, may range in severity from mild to life-threatening. Therefore, consider this diagnosis in patients who present with diarrhea subsequent to administration of antibacterial agents.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After establishing diagnosis of pseudomembranous colitis, initiate therapeutic measures. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consider management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug effective against *C. difficile*.

PRECAUTIONS: *GENERAL:* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.*, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

Rare cases reported of sonographic abnormalities seen in the gallbladder; patients may also have symptoms of gallbladder disease. These abnormalities, variously described as sludge, precipitations, echoes with shadows, may be misinterpreted as concretions. Chemical nature of sonographically-detected material not determined. Condition appears to be transient and reversible upon discontinuation of Rocephin and conservative management. Therefore, discontinue Rocephin if signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above develop.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

PREGNANCY: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

NURSING MOTHERS: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section. *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Rocephin should not be administered to hyperbilirubinemic neonates, especially prematures.

ADVERSE REACTIONS: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration.

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESTINAL—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

HEPATIC—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

RENAL—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%).

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%).

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours.

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days; in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone; piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone; bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION).

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2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.2 gm dextrose hydrous, USP added.

NOTE: Rocephin in the frozen state should not be stored above -20°C.

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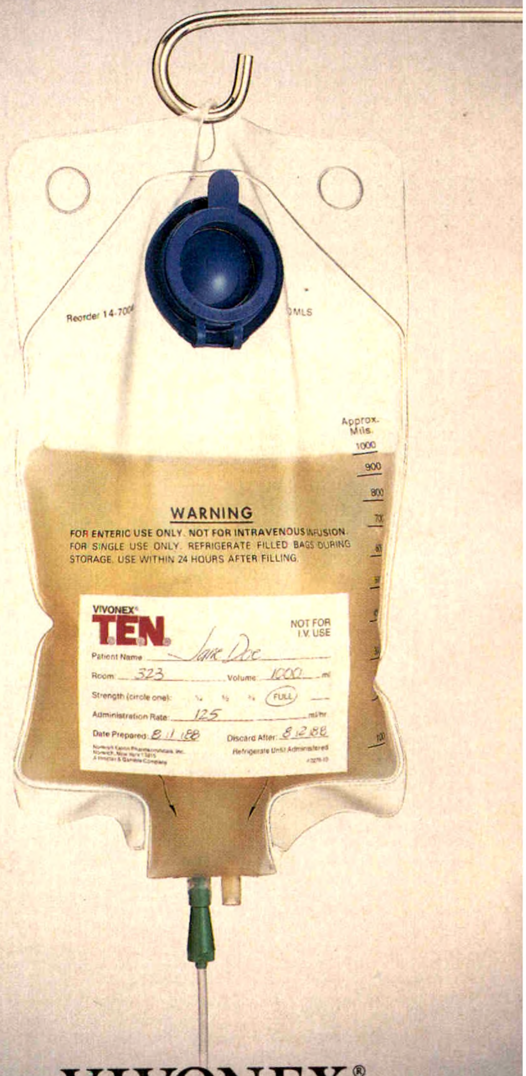
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References: 1. Andrassy RJ: Preserving the gut mucosal barrier and enhancing immune response. *Contemp Surg* 1988;32(2-A):21-27. **2.** Hoover HC Jr: Enteral elemental nutrition in major abdominal surgery. *Contemp Surg* 1986;28(4-A):12-17. **3.** Bower RH, Talamini MA, Sax HC, et al: Postoperative enteral vs parenteral nutrition: A randomized controlled trial. *Arch Surg* 1986; 121:1040-1045. **4.** Souba WW, Smith RJ, Wilmore DW: Glutamine metabolism by the intestinal tract. *JPEN* 1985;9:608-617. **5.** Fox AD, Kripke SA, Berman JR, et al: Reduction of the severity of enterocolitis by glutamine-supplemented enteral diets. *Surgical Forum* 1987;38:43-44. **6.** Hwang TL, O'Dwyer ST, Smith RJ: Preservation of small bowel mucosa using glutamine-enriched parenteral nutrition. *Surgical Forum* 1986;37:56-57.

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Frederick W. Clevenger, MD; Jose A. Acosta, MD; Turner M. Osler, MD;
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- Barotrauma is a significant potential complication of HFJV in patients with noncompliant lungs.

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Anton J. Bilchik, MD; Karl A. Zucker, MD; Thomas E. Adrian, PhD, MRC(Path);
Irvin M. Modlin, MD, PhD, Baltimore, Md
- Blockade of low concentrations of CCK in the pancreatitis model promotes a beneficial effect.

Analysis of the Transition to Percutaneous Placement of Greenfield Filters 1550
Robert J. Hye, MD; Alfred T. Mitchell, MD; Christopher E. Dory, MD;
Julie A. Freischlag, MD; Anne C. Roberts, MD, San Diego, Calif
- Cost, ease of insertion, and safety make percutaneous insertion of the Greenfield filter the procedure of choice.

Percutaneous Catheter Drainage of Infected Pancreatic and Peripancreatic Fluid Collections 1554
David B. Adams, MD; Tracy S. Harvey, MD; Marion C. Anderson, MD, Charleston, SC
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- Neuropeptide Y inhibits VIP-stimulated short circuit changes by a tetrodotoxin insensitive mechanism that decreases tissue levels of cAMP.

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R. Matthew Walsh, MD, Maywood, Ill;
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- Arteries with hemodynamically significant stenoses from intimal flaps warrant repair; with lesser intimal flaps, repair may not be required.

The Effect of Intestinal Resection and Urogastrone on Intestinal Regeneration 1617
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- Persistent cell loss in response to rotational shear differs in identical rates of pulsatile shear where loss approached zero after 15 minutes.

CLINICAL NOTE

Surgical Aspects of Sclerosing Encapsulating Peritonitis
Dilip S. Kittur, MD, ScD, Baltimore, Md;
Subhash W. Korpe, MD, Bombay, India;
Roman E. Raytch, MD; Gardner W. Smith, MD, Baltimore, Md
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Reference: 1. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *New Engl J Med.* 1990;322:352-358.

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INDICATIONS AND USAGE: ERGAMISOL (levamisole hydrochloride) is only indicated as adjuvant treatment in combination with fluorouracil after surgical resection in patients with Dukes' stage C colon cancer.

CONTRAINDICATIONS: ERGAMISOL (levamisole hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or its components.

WARNINGS: ERGAMISOL (levamisole hydrochloride) has been associated with agranulocytosis, sometimes fatal. The onset of agranulocytosis is frequently accompanied by a flu-like syndrome (fever, chills, etc.); however, in a small number of patients it is asymptomatic. A flu-like syndrome may also occur in the absence of agranulocytosis. It is essential that appropriate hematological monitoring be done routinely during therapy with ERGAMISOL and fluorouracil. Neutropenia is usually reversible following discontinuation of therapy. Patients should be instructed to report immediately any flu-like symptoms.

Higher than recommended doses of ERGAMISOL may be associated with an increased incidence of agranulocytosis, so the recommended dose should not be exceeded.

The combination of ERGAMISOL and fluorouracil has been associated with frequent neutropenia, anemia and thrombocytopenia.

PRECAUTIONS: Before beginning this combination adjuvant treatment, the physician should become familiar with the labeling for fluorouracil.

Information for Patients: The patient should be informed that if flu-like symptoms or malaise occurs, the physician should be notified immediately.

Drug Interactions: ERGAMISOL (levamisole hydrochloride) has been reported to produce "ANTABUSE®"-like side effects when given concomitantly with alcohol. Concomitant administration of phenytoin and ERGAMISOL plus fluorouracil has led to increased plasma levels of phenytoin. The physician is advised to monitor plasma levels of phenytoin and to decrease the dose if necessary.

Laboratory Tests: On the first day of therapy with ERGAMISOL/fluorouracil, patients should have a CBC with differential and platelets, electrolytes and liver function tests performed. Thereafter, a CBC with differential and platelets should be performed weekly prior to each treatment with fluorouracil with electrolytes and liver function tests performed every 3 months for a total of one year. Dosage modifications should be instituted as follows: If WBC is 2500-3500/mm^3 defer the fluorouracil dose until WBC is > 3500/mm^3. If WBC is < 2500/mm^3, defer the fluorouracil dose until WBC is > 3500/mm^3; then resume the fluorouracil dose reduced by 20%. If WBC remains < 2500/mm^3 for over 10 days despite deferring fluorouracil, discontinue administration of ERGAMISOL. Both drugs should be deferred unless enough platelets are present (≥ 100,000/mm^3).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate animal carcinogenicity studies have not been conducted with levamisole. Studies of levamisole administered in drinking water at 5, 20, and 80 mg/kg/day to mice for up to 18 months or administered to rats in the diet at 5, 20, and 80 mg/kg/day for 24 months showed no evidence of neoplastic effects. These studies were not conducted at the maximum tolerated dose, therefore the animals may not have been exposed to a reasonable drug challenge. No mutagenic effects were demonstrated in dominant lethal studies in male and female mice, in an Ames test, and in a study to detect chromosomal aberrations in cultured peripheral human lymphocytes.

Adverse effects were not observed on male or female fertility when levamisole was administered to rats in the diet at doses of 2.5, 10, 40, and 160 mg/kg. In a rat gavage study at doses of 20, 60, and 180 mg/kg, the copulation period was increased, the duration of pregnancy was slightly increased, and fertility, pup viability and weight, lactation index, and number of fetuses were decreased at 60 mg/kg. No negative reproductive effects were present when the offspring were allowed to mate and litter.

Pregnancy: Pregnancy Category C: Teratogenicity studies have been performed in rats and rabbits at oral doses up to 180 mg/kg. Fetal malformations were not observed. In rats, embryotoxicity was present at 160 mg/kg and in rabbits, significant embryotoxicity was observed at 180 mg/kg. There are no adequate and well-controlled studies in pregnant women and ERGAMISOL should not be administered unless the potential benefits outweigh the risks. Women taking the combination of ERGAMISOL and fluorouracil should be advised not to become pregnant.

Nursing Mothers: It is not known whether ERGAMISOL is excreted in human milk; it is excreted in cows' milk. Because of the potential for serious adverse reactions in nursing infants from ERGAMISOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ERGAMISOL in children have not been established.

ADVERSE REACTIONS: Almost all patients receiving ERGAMISOL (levamisole hydrochloride) and fluorouracil reported adverse experiences. Tabulated below is the incidence of adverse experiences that occurred in at least 1% of patients enrolled in two clinical trials who were adjuvantly treated with either ERGAMISOL or ERGAMISOL plus fluorouracil following colon surgery. In the larger clinical trial, 66 of 463 patients (14%) discontinued the combination of ERGAMISOL plus fluorouracil because of adverse reactions. Forty-three of these patients (9%) developed isolated or a combination of gastrointestinal toxicities (e.g. nausea, vomiting, diarrhea, stomatitis and anorexia). Ten patients developed rash and/or pruritus. Five patients discontinued therapy because of flu-like symptoms or fever with chills; ten patients developed central nervous system symptoms such as dizziness, ataxia, depression, confusion, memory loss, weakness, inability to concentrate, and headache; two patients developed reversible neutropenia and sepsis; one patient because of thrombocytopenia; one patient because of hyperbilirubinemia. One patient in the ERGAMISOL plus fluorouracil group developed agranulocytosis and sepsis and died.

In the ERGAMISOL alone arm of the trial, 15 of 310 patients (4.8%) discontinued therapy because of adverse experiences. Six of these (2%) discontinued because of rash, six because of arthralgia/myalgia, and one each for fever and neutropenia, urinary infection, and cough.

For medical questions, call 1-800-253-3682 (9 AM-5 PM Eastern Time).

Adverse experience	ERGAMISOL N = 440 %	ERGAMISOL plus fluorouracil N = 599 %
Gastrointestinal		
Nausea	22	65
Diarrhea	13	52
Stomatitis	3	39
Vomiting	6	20
Anorexia	2	6
Abdominal pain	2	5
Constipation	2	3
Flatulence	<1	2
Dyspepsia	<1	1
Hematological		
Leukopenia		
<2000/mm^3	<1	1
≥2000 to <4000/mm^3	4	19
≥4000/mm^3	2	33
unscored category	0	<1
Thrombocytopenia		
<50,000/mm^3	0	0
≥50,000 to <130,000/mm^3	1	8
≥130,000/mm^3	1	10
Anemia	0	6
Granulocytopenia	<1	2
Epistaxis	0	1
Skin and Appendages		
Dermatitis	8	23
Alopecia	3	22
Pruritus	1	2
Skin discoloration	0	2
Urticaria	<1	0
Body as a Whole		
Fatigue	6	11
Fever	3	5
Rigors	3	5
Chest pain	<1	1
Edema	1	1
Resistance Mechanisms		
Infection	5	12
Special Senses		
Taste Perversion	8	8
Altered sense of smell	1	1
Musculoskeletal System		
Arthralgia	5	4
Myalgia	3	2
Central and peripheral nervous system		
Dizziness	3	4
Headache	3	4
Paresthesia	2	3
Ataxia	0	2
Psychiatric		
Somnolence	3	2
Depression	1	2
Nervousness	1	2
Insomnia	1	1
Anxiety	1	1
Forgetfulness	0	1
Vision		
Abnormal tearing	0	4
Blurred vision	1	2
Conjunctivitis	<1	2
Liver and biliary system		
Hyperbilirubinemia	<1	1

In worldwide experience with ERGAMISOL, less frequent adverse experiences included exfoliative dermatitis, periorbital edema, vaginal bleeding, anaphylaxis, confusion, convulsions, hallucinations, impaired concentration, renal failure, elevated serum creatinine, and increased alkaline phosphatase. An encephalopathy - like syndrome has been reported in patients treated with ERGAMISOL.

The following additional adverse experiences have been reported for fluorouracil alone: esophagopharyngitis, pancytopenia, myocardial ischemia, angina, gastrointestinal ulceration and bleeding, anaphylaxis and generalized allergic reactions, acute cerebellar syndrome, nystagmus, dry skin, fissuring, photosensitivity, lacrimal duct stenosis, photophobia, euphoria, thrombophlebitis, and nail changes.

HOW SUPPLIED: ERGAMISOL (levamisole hydrochloride) is available in white, coated tablets containing the equivalent of 50 mg of levamisole base, debossed "JANSSEN" and "L" "50."

They are supplied in blister packages of 36 tablets (NDC 50458-270-36).

Store at room temperature, 15°-30°C (59°-86°F). Protect from moisture.

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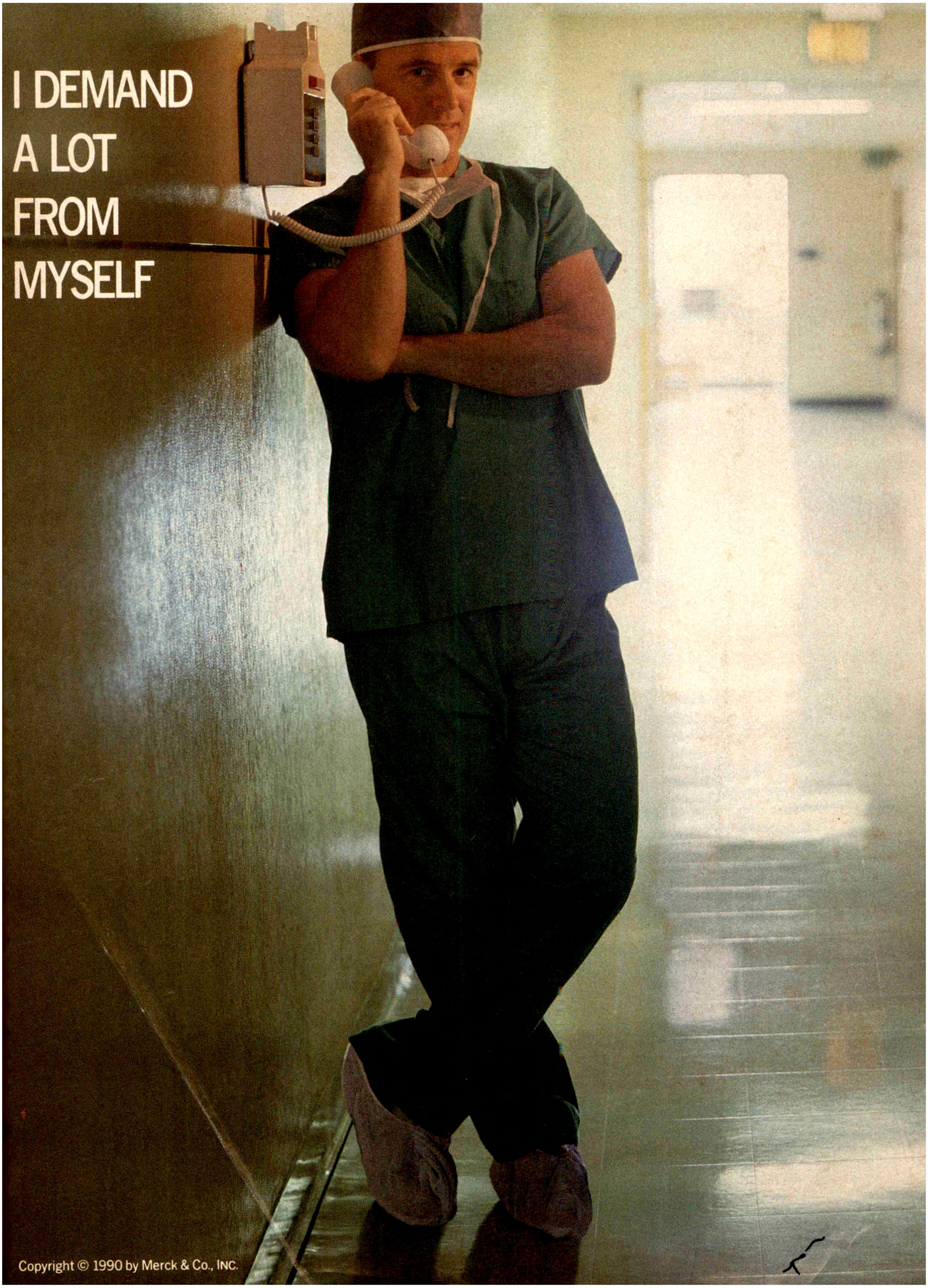

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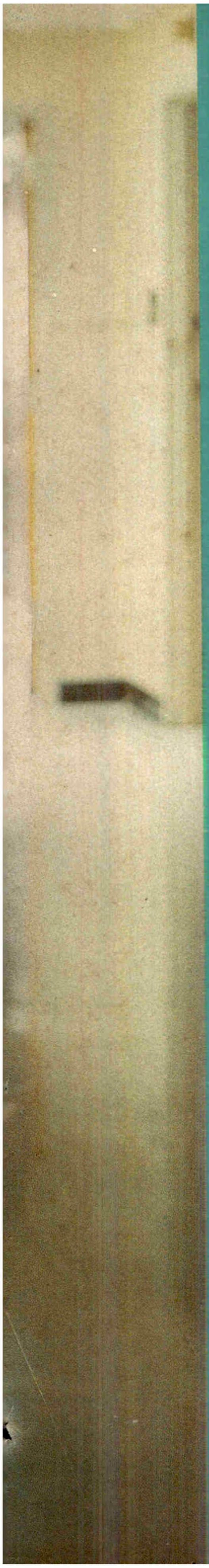

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MEFOXIN

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BALANCED COVERAGE† WITH

MEFOXIN® IV/IM

(CEFOXITIN SODIUM | MSD)

†*in vitro* activity against indicated aerobes and anaerobes

MEFOXIN is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

MEFOXIN is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Streptococcus faecalis*) and many strains of *Enterobacter cloacae.* Methicillin-resistant staphylococci are almost uniformly resistant to MEFOXIN.

*in infections caused by indicated organisms at indicated sites

Please see following page for a Brief Summary of Prescribing Information.

BALANCED COVERAGE† WITH

MEFOXIN® IV/IM

(CEFOXITIN SODIUM|MSD)

†*in vitro* activity against indicated aerobes and anaerobes

Indications and Usage: *Treatment*—Serious infections caused by susceptible strains of the designated microorganisms in the following diseases:

LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by *Streptococcus pneumoniae*, other streptococci (excluding enterococci, e.g., *Strep. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Hemophilus influenzae*, and *Bacteroides* species.

GENITOURINARY INFECTIONS. Urinary tract infections caused by *E. coli*, *Klebsiella* species, *Proteus mirabilis*, indole-positive *Proteus* (which include the organisms now called *Morganella morganii* and *Proteus vulgaris*), and *Providencia* species (including *Providencia rettgeri*). Uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing).

INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,* and *Clostridium* species.

GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by *E. coli*, *N. gonorrhoeae* (penicillinase and non-penicillinase producing), *Bacteroides* species including the *B. fragilis* group,* *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and group B streptococci.

SEPTICEMIA caused by *Strep. pneumoniae*, *Staph. aureus* (penicillinase and non-penicillinase producing), *E. coli*, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.*

BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,* *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to cefoxitin.

Prevention—Prophylactic use in surgical procedures (e.g., hysterectomy, gastrointestinal surgery, cesarean section, transurethral prostatectomy) classified as contaminated or potentially contaminated or in patients in whom subsequent infection at the operative site would present a serious risk, e.g., prosthetic arthroplasty.

MEFOXIN® (Cefoxitin Sodium, MSD) usually should be given ½ to 1 hour before surgery and should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection. However, in patients undergoing prosthetic arthroplasty, it is recommended that MEFOXIN be continued for 72 hours after the surgical procedure. If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so appropriate treatment may be instituted.

Contraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, from mild to life-threatening in severity, has been reported with virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis when diarrhea develops in association with antibiotic use. Broad-spectrum antibiotics alter normal flora of colon and may permit overgrowth of clostridia; a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis. Mild cases may respond to drug discontinuance alone; in more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and use of a drug such as oral vancomycin; isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—Total daily dose should be reduced in patients with reduced urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur from usual doses. Prescribe with caution in patients with a history of gastrointestinal disease, particularly colitis. Prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures.

Drug Interactions—Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Drug/Laboratory Test Interactions—High concentrations (>100 mcg/mL) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. High concentrations may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction and produce false increases of modest degree in levels reported. A false-positive reaction for glucose in urine has been observed with CLINITEST** reagent tablets.

Carcinogenesis, Mutagenesis, Fertility Impairment—No long-term animal study has been performed on carcinogenic or mutagenic potential. Rat studies at approximately three times maximum recommended human dosage revealed no effects on fertility or mating ability.

Pregnancy Category B—Reproduction studies in rats and mice did not reveal teratogenic or fetal toxic effects, although fetal weights were slightly decreased. In rabbits, cefoxitin was associated with a high incidence of abortion and maternal death, neither considered teratogenic. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Excreted in human milk: Exercise caution.

Pediatric Use—Safety and efficacy in infants from birth to three months have not yet been established. In children three months and older, higher doses have been associated with increased incidence of eosinophilia and elevated SGOT.

Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently.

Local Reactions—Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. *Allergic Reactions*—Rash (including exfoliative dermatitis), pruritus, eosinophilia, fever, and other allergic reactions including anaphylaxis. *Cardiovascular*—Hypotension. *Gastrointestinal*—Diarrhea, including documented pseudomembranous colitis during or after treatment, and, rarely, nausea and vomiting. *Blood*—Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hemolytic anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may develop in some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase; jaundice. *Renal Function*—Elevations in serum creatinine and/or blood urea nitrogen levels and, rarely, acute renal failure.

Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. The total daily dosage in infants and children should not exceed 12 grams.

How Supplied: Sterile cefoxitin sodium in vials, infusion bottles, and ADD-Vantage®† vials containing 1 gram or 2 grams cefoxitin equivalent and in 10-gram bulk bottles.

B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus

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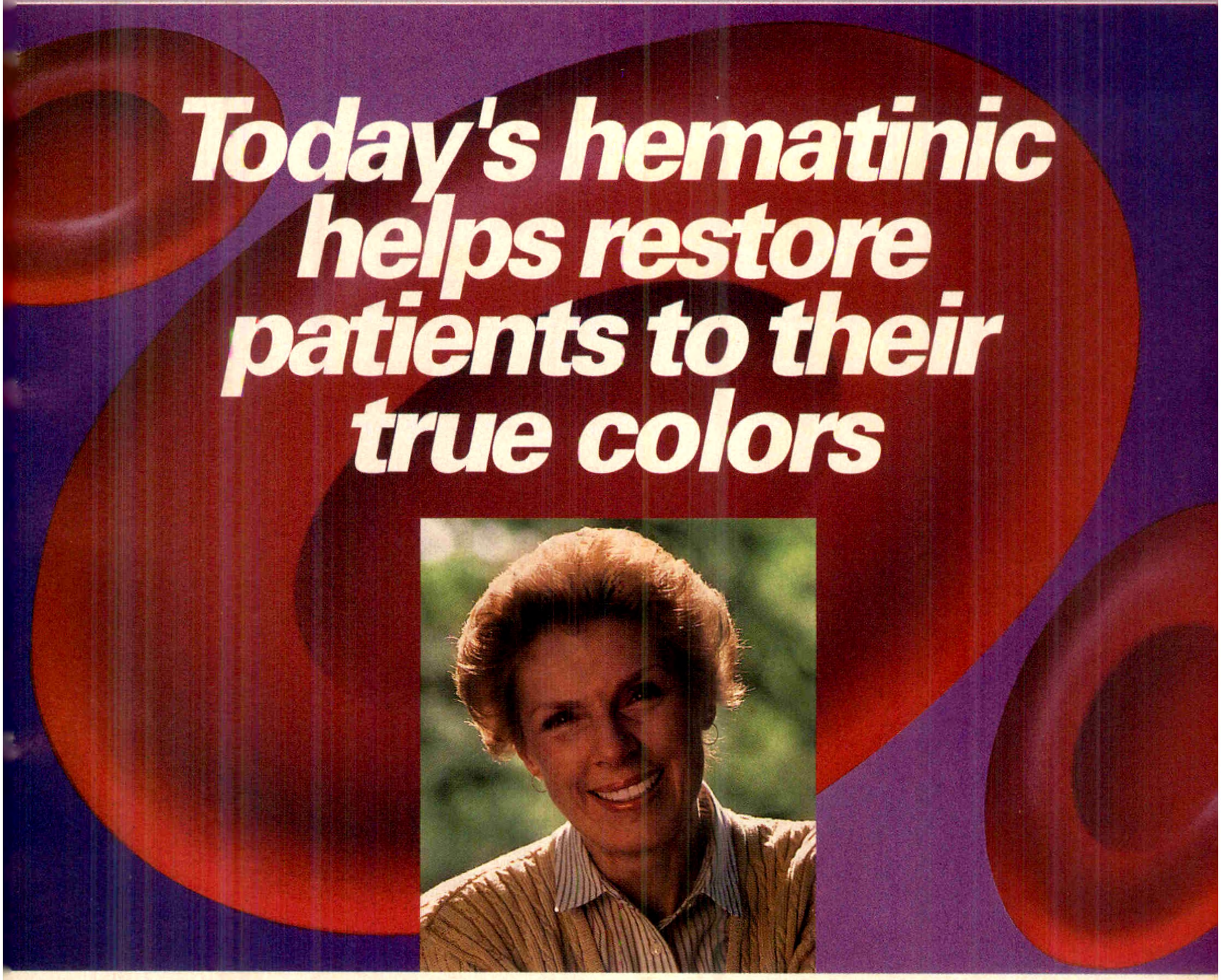

Today's hematinic helps restore patients to their true colors

Anemia is a growing problem — beyond hematologic parameters

The Elderly
☐ Risk for anemia increases with chronic disease, concomitant medication, G.I. surgery[1-3]

Surgical Patients
☐ Use of autologous transfusions[4] may increase anemia

Limited Heme Iron Consumption
☐ May predispose patients to iron deficiency anemia,[5] and strict vegetarianism may help induce vitamin B_{12} deficiency[6]

The complete hematinic, complete with intrinsic factor

TRINSICON's unique formulation provides the necessary nutrients for successful erythropoiesis

☐ Vitamin B_{12} with Intrinsic Factor
☐ Iron ☐ Folic acid ☐ Other B-complex vitamins
☐ Vitamin C, which activates folic acid and increases iron absorption

Effective in the treatment of nutritionally responsive anemias

☐ Iron deficiency ☐ Vitamin B_{12} deficiency
☐ Folate deficiency

(The specific cause[s] of the anemia should always be investigated.)

TRINSICON® **THE COMPLETE HEMATINIC**
Hematinic Concentrate with Intrinsic Factor

Please see Brief Summary of Prescribing Information on adjacent page.

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Brief Summary

TRINSICON®

Hematinic Concentrate with Intrinsic Factor

A Highly Potent Oral Antianemia Preparation

INDICATIONS AND USAGE: TRINSICON® is a multifactor preparation effective in the treatment of anemias that respond to oral hematinics, including pernicious anemia and other megaloblastic anemias and also iron-deficiency anemia. Therapeutic quantities of hematopoietic factors that are known to be important are present in the recommended daily dose. **CONTRAINDICATIONS:** Hemochromatosis and hemosiderosis are contraindications to iron therapy. **PRECAUTIONS: General:** Anemia is a manifestation that requires appropriate investigation to determine its cause or causes. Folic acid *alone* is unwarranted in the treatment of pure vitamin B$_{12}$ deficiency states, such as pernicious anemia. Folic acid may obscure pernicious anemia in that the blood picture may revert to normal while neurolological manifestations remain progressive. As with all preparations containing intrinsic factor, resistance may develop in some cases of pernicious anemia to the potentiation of absorption of physiologic doses of vitamin B$_{12}$. If resistance occurs, parenteral therapy or oral therapy with so-called massive doses of vitamin B$_{12}$ may be necessary for adequate treatment of the patient. No single regimen fits all cases, and the status of the patient observed in follow-up is the final criterion for adequacy of therapy. Periodic clinical and laboratory studies are considered essential and are recommended. **Pregnancy:** ***Pregnancy Category C:*** Animal reproduction studies have not been conducted with TRINSICON® It is also not known whether TRINSICON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRINSICON should be given to a pregnant woman only if clearly needed. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRINSICON is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 10 have not been established. **ADVERSE REACTIONS:** Rarely, iron in therapeutic doses produces gastrointestinal reactions, such as diarrhea or constipation. Reducing the dose and administering it with meals will minimize these effects in the iron-sensitive patient. In extremely rare instances, skin rash suggesting allergy has been noted following the oral administration of liver-stomach material. Allergic sensitization has been reported following both oral and parenteral administration of folic acid. **OVERDOSAGE: Symptoms:** Those of iron intoxication, which may include pallor and cyanosis, vomiting, hematemesis, diarrhea, melena, shock, drowsiness, and coma. **Treatment:** For specific therapy, exchange transfusion and chelating agents. For general management, gastric and rectal lavage with sodium bicarbonate solution or milk, administration of intravenous fluids and electrolytes, and use of oxygen. **DOSAGE AND ADMINISTRATION:** One capsule twice a day. (Two capsules daily produce a standard response in the average uncomplicated case of pernicious anemia.)

Manufactured for
Russ Pharmaceuticals, Birmingham, AL 35242
by Central Pharmaceuticals, Seymour, IN 47274

June 1990

Russ Pharmaceuticals, Inc.

Birmingham, AL 35242
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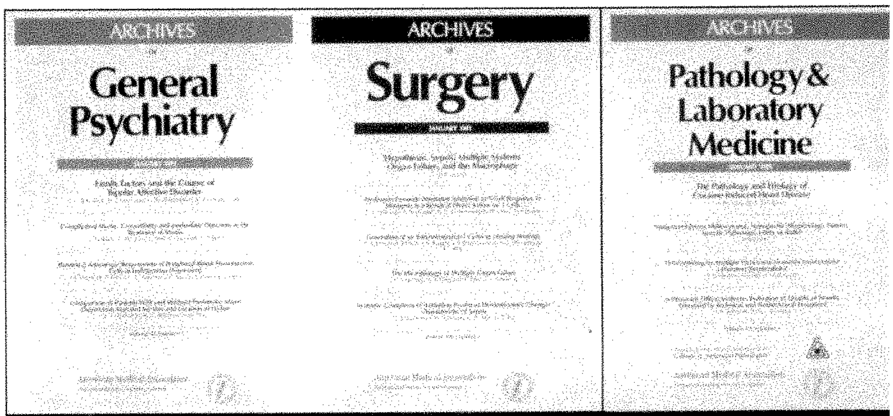

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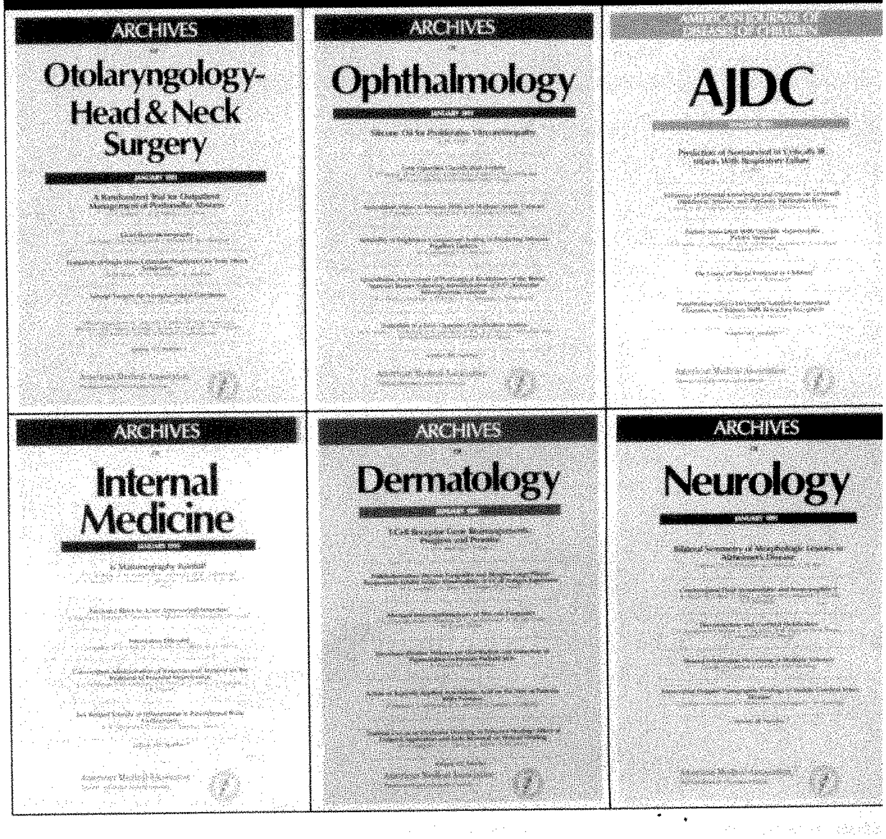

Commentary

Selective Bowel Decontamination

Less Enthusiasm and More Study Is in Order

Selective bowel decontamination is a method of antibiotic prophylaxis aimed at reducing the incidence of nosocomial pneumonia and mortality in intubated ventilated patients in the intensive care unit (ICU). It involves the administration of short-term parenteral antibiotics coupled with the application of antibiotic paste to the oral mucous membranes and liquid antibiotics administered via a nasogastric tube for up to 4 weeks. The underlying hypothesis involves these assumptions: First, intubated ventilated patients in the ICU have an increased incidence of nosocomial pneumonia as well as other infections. Second, the bacteria causing these infections are endogenous gram-negative aerobes originating in the gut. Third, control of these infections can be accomplished through antibiotic prophylaxis with no adverse impact on the bacterial ecology of the patient or the ICU environment. Fourth, and most important, use of this complex regimen of antibiotic prophylaxis in intubated, ventilated patients in the ICU results in a decrease in nosocomial pneumonia and other infections and in consequent mortality. None of these assumptions has been demonstrated unequivocally to be true.

Although the originators of selective gut decontamination[1,2] have not conducted a controlled clinical trial to document the efficacy of the method, several other investigators have completed such trials. Growing enthusiasm for implementation of selective bowel decontamination[3,4] suggests that evaluation of this evidence is in order. Only a summary can be included here; interested surgeons should read the original reports for more details.

Eight prospective clinical trials have been conducted (B. Rowlands, P. Blair, written communication, June 1990).[5-11] They were all structured so that subjects undergoing selective bowel decontamination were compared randomly with untreated controls. The patients in both the control and treatment groups were intubated, ventilated patients in the ICU; infections appearing within the first 48 hours of hospitalization usually were discounted as being of community origin. Although the exact antibiotic regimen recommended by Stoutenbeek and colleagues[12,13] was not always precisely followed, the antibiotic therapy used in each trial was appropriate, in my judgment, to accomplish the major objectives.

In these clinical trials, a diagnosis of nosocomial pneumonia was made if a new infiltrate that was not reversible by physiotherapy appeared on the chest roentgenogram and was accompanied by purulent tracheobronchial secretions obtained by endotracheal suctioning; supporting clinical features included the presence of fever, an elevated or markedly depressed leukocyte count, and evidence of hypoxia on blood gas analysis. The outcomes of these trials demonstrated a significant decrease in the occurrence of nosocomial pneumonia; often urinary tract infections and other similar afflictions were also reduced in incidence. However, mortality usually was not affected. Meta-analysis of the data from the prospective trials confirmed the lack of a significant effect of selective bowel decontamination on mortality.

The major problem with all of the clinical trials of selective bowel decontamination is a lack of blinding. Conscious or unconscious bias in classifying patients and determining outcomes is, therefore, a potential difficulty. Diagnosing nosocomial pneumonia, and distinguishing it from tracheobronchitis, atelectasis, and adult respiratory distress syndrome based on the diagnostic criteria listed above, is a subjective clinical exercise. The decision that an infiltrate on a chest roentgenogram represents only atelectasis rather than pneumonia, particularly when the decision is made retrospectively, may be subtly influenced by knowledge of the treatment employed. The opportunities for bias in an unblinded clinical trial are readily apparent, and conclusions drawn from such trials are very uncertain.

Additionally, the occurrence of a Hawthorn effect in the reported clinical trials is a real possibility. Support for this assertion comes from the report by Brun-Buisson and colleagues,[14] who conducted a trial of selective bowel decontamination in an attempt to control an outbreak of infections due to a multiresistant *Klebsiella*. Data on the baseline incidence of nosocomial pneumonia in their ICU, and of the effects of instituting their study comparing antibiotic prophylaxis against untreated controls, was recorded. During the study, both treated and untreated patients had a marked decrease in the incidence of nosocomial pneumonia and other infections compared with the baseline period. Thus, just being a subject in the study had a salutary effect, even when no antibiotics were administered. Such an observation reinforces the need for conducting clinical trials of selective bowel decontamination on a blinded basis. Blinding is not difficult to arrange; it involves applying to the untreated control group the oral paste and liquid vehicles used to carry antibiotics in the treated group of patients.

Another problem in the clinical trials reported to date is the observation that selective bowel decontamination does not improve mortality. Selective bowel decontamination does reduce the risk of nosocomial pneumonia, but patients die nonetheless of other causes. This situation is reminiscent of the controlled trials of prophylactic portacaval shunting reported some years ago.[15,16] Prophylactic shunting prevented the undesirable effect of bleeding from esophageal varices, but the research subjects died anyway at the same rate as controls due to other causes, principally liver failure. Prophylactic portacaval shunting has, quite properly, not become an accepted clinical treatment option. Similarly, unless selective bowel decontamination can be demonstrated to have a positive effect on the overall mortality risk of patients in the ICU, it becomes merely an exercise in changing the mode of the patient's death and probably is not worth the effort.

There are other, more minor objections to the application of selective gut decontamination at this stage of our understanding. Although some reports[17,18] have supported the notion that the necessarily prolonged use of this technique of antibiotic prophylaxis does not lead to the emergence of resistant organisms, my view is that such a fortuitous outcome cannot be sustained over time. The need to treat patients with antibiotics for more than 1 or 2 days clearly involves a risk. If the past is any guide to the future, it is inevitable that bacteria eventually will become resistant to the antibiotics employed for selective bowel decontamination. In addition, evidence is beginning to emerge that although selective bowel decontamination reduces the incidence of gram-negative infections, the incidence of gram-positive colonization[19] and translocation[20] increases with this prophylactic treatment.

So, what is the present position? Selective bowel decontamination presents an attractive hypothesis, but one that is not yet proved. The flawed evidence available to date suggests that there may be positive effects from use of this prophylactic antibiotic regimen, but the data do not establish such as fact. What is needed, of course, is a large, *blinded* clinical trial. Until the results of such a trial are available, selective bowel decontamination should be viewed as an unproved and experimental method of therapy, and patients should not be subjected to its potential risks outside the structure of a controlled clinical trial.

Robert E. Condon, MD, MS
Milwaukee, Wis

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Reappraisal of Pancreatic and Duodenal Injury Management Based on Injury Severity

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• We evaluated the effectiveness of treatment protocols for pancreatic and duodenal injuries according to the severity of injury. Of 81 patients, 65 survived initial injury. Pancreatic injuries without ductal involvement occurred in 21 patients and were treated by drainage. No late deaths occurred. Pancreatic injuries with ductal disruption occurred in 18 patients and were treated by pancreatic resection. Abscesses developed in seven (39%) of the patients, but no late deaths occurred. Nineteen patients had duodenal injuries without pancreatic injury, and no duodenal complications occurred. Simple closure sufficed for injuries affecting up to 40% of the duodenal circumference. Wounds affecting up to 40% of the duodenal circumference can be treated by suture closure alone. Adjunctive duodenal tube decompression should be reserved for wounds affecting greater than 40% of the duodenal circumference, closure under tension, and associated injuries to the head of the pancreas. Pyloric exclusion was rarely necessary in our patients.

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Management of pancreatic and duodenal injuries remains controversial, without a consensus for optimal treatment. The percentage of patients with duodenal injuries treated by primary duodenal closure alone,[1-3] closure with decompressive tube duodenostomy,[4] and pyloric exclusion varies widely from institution to institution.[5] Adjuncts to primary closure are used extensively at some institutions, but rarely at others. Management of distal pancreatic wounds is less controversial,[3] but management of proximal pancreatic ductal injuries and combined pancreaticoduodenal injuries remains problematic. Investigators at our institution[6,7] have proposed protocols based on the severity of pancreatic and duodenal injury in an effort to standardize management of these wounds. This study was undertaken to determine the effectiveness of these protocols in treating patients with pancreatic, duodenal, or combined pancreaticoduodenal wounds.

MATERIALS AND METHODS

We retrospectively studied 81 consecutive patients with pancreatic, duodenal, or combined pancreaticoduodenal injuries who were treated at Humana Hospital University, Louisville, Ky, from 1984 to 1989. There were 60 men and 21 women (mean age, 33 years). Indications for operation, severity of injury, associated injuries, operative procedures, complications, and mortality were tabulated.

The management protocol for duodenal injuries was based on previously described injury grades.[6] According to this protocol, duodenal hematomas and serosal tears (grade I) were to be treated with nasogastric decompression alone. Simple lacerations affecting less than 20% of the duodenal circumference (grade II) were to be closed in two layers without tube decompression. Duodenal defects affecting between 20% and 70% of the duodenal circumference (grade III) were to be closed in two layers, with tube decompression as an adjunct. Defects affecting greater than 70% of the duodenal circumference (grade IV) were to be managed by more complex methods, including pyloric exclusion.

Pancreatic injuries were graded according to a previously described injury classification.[7] According to this protocol, pancreatic contusions (grade I) were to be treated by suction drainage alone and minor pancreatic parenchymal lacerations (grade II) were to be treated by débridement and suction drainage. When pancreatic ductal injury was suspected (grade III), distal pancreatic resection was to be employed. Severe crush injuries (grade IV) were to be treated by débridement, drainage, or resection, depending on location and associated injuries.

Combined pancreaticoduodenal injuries were classified according to the scheme proposed by Moore and Moore,[8] who classified grade I injuries as partial-thickness duodenal injuries without pancreatic ductal involvement. Grade II wounds were full-thickness duodenal wounds without pancreatic ductal involvement, grade III injuries were full-thickness duodenal wounds accompanied by distal pancreatic ductal injury; grade IV injuries included duodenal wounds that affected greater than 20% of duodenal circumference and that involved a major proximal pancreatic ductal disruption; and grade V injuries were classified as causing devitalizing injury to both duodenum and pancreas.

We have treated injuries from grade I through grade IV by treating their component parts separately, as described with isolated duodenal or pancreatic injury. Grade V injuries were treated by a more aggressive operation, including pyloric exclusion, duodenal diverticulization, or resection, in the most severe cases.

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Table 1.—Associated Injuries

	Pancreas	Duodenum	Combined
Stomach	16	3	3
Small bowel	3	5	4
Colon	9	10	3
Gallbladder	2	3	3
Liver	18	5	3
Abdominal vascular	11	5	10
Kidney	11	3	8
Diaphragm	5	0	3
Heart	1	0	2
Spleen	14	0	4
Other	10	5	0

Table 2.—Duodenal Injury Management (n = 19)*

Injury or Grade	% Circumference Lost	Nasogastric Compression	Closure Alone	Closure and Decompression
I	0 (partial thickness)	3	0	0
II	<20	0	5	3
III	30	0	1	1
	40	0	2	1
	50	0	0	2
	60	0	0	0
	70	0	0	1

*Excludes four early deaths unrelated to duodenal wound management. There were no late deaths, intra-abdominal abscesses, or duodenal fistulas in these patients.

RESULTS

Duodenal injury occurred in 23 patients (28%), pancreatic injury in 47 patients (58%), and combined pancreaticoduodenal injury in 11 patients (14%). Forty-eight patients sustained penetrating injuries, including 32 gunshot and 16 stab wounds. Blunt injuries occurred in 33 patients. These injuries resulted from automobile accidents in 26 cases and from motorcycle accidents in four cases. Three patients were injured in a fall, a boating accident, and a farm-related mishap. The Injury Severity Score was 24 ± 13 (SD) for survivors and 56 ± 16 for those who died.

Of the 81 patients studied, 16 (20%) died; 14 (88%) of these 16 died of hemorrhagic shock. Head injury and respiratory failure caused the other two deaths. All deaths occurred within 24 hours of admission, and these patients were excluded from further analysis. Associated injuries are listed in Table 1.

Exploratory laparotomy was performed on all patients with abdominal gunshot wounds. Fascial penetration was the primary reason for exploration in the 16 patients with stab wounds. Thirty-three patients underwent surgery following blunt abdominal trauma. Of these, 25 underwent surgery because of positive diagnostic peritoneal lavage, defined as erythrocyte counts greater than 100 000/mm^3 or leukocyte counts greater than 500/mm^3. The remaining eight patients had abdominal tenderness or other findings suggestive of intra-abdominal injury. A 48-hour delay in diagnosis occurred in one patient from the latter group who subsequently developed a pancreatic abscess.

Twenty-one (54%) of 39 patients with pancreatic injuries, but no duodenal involvement, had grade I or II injuries without evidence of ductal injury and were treated by suction drainage alone. Four (19%) of the 21 subsequently developed intra-abdominal abscesses, and five (24%) developed pancreatic fistulas. We defined a pancreatic fistula as an effluent from the drain site with an amylase level higher than serum and a volume greater than 100 mL that persisted for at least a week. Three of the 21 patients had both an abscess and a fistula. Eighteen (46%) of the 39 patients had grade III or IV pancreatic injuries with ductal disruption that were treated by distal pancreatectomy; seven (39%) of the 18 patients developed intra-abdominal abscesses, and one (6%) developed a pancreatic fistula. All fistulas closed without operation. Intra-abdominal abscess did not correlate with the severity of pancreatic injury or with the operative technique employed, but did correlate with associated hollow viscus injury. Eight (44%) of 18 patients with pancreatic injuries and hollow viscus injuries developed intra-abdominal abscesses, compared with three (14%) of 21 patients without hollow viscus injuries ($P<.05$). Hollow viscus injuries occurred in patients with intra-abdominal abscesses in the stomach (four patients), the colon (two patients), and the small bowel (two patients). Additional complications in the distal pancreatectomy group included one wound infection, one case of pancreatitis, and one case of exocrine insufficiency after an 85% distal pancreatectomy.

Nineteen patients had duodenal injuries without pancreatic involvement (Table 2). Three patients with duodenal hematomas (grade I) were treated, without complication, with nasogastric decompression alone. The protocol for treatment of duodenal injuries was not followed strictly. Eight (42%) of the patients had grade II injuries. Five were treated by two-layer closure alone, and three had additional triple-tube decompression. Eight patients had grade III injuries; three were treated by primary closure alone, and five had adjunctive use of triple-tube decompression. The duodenal defects of these patients are grouped by severity in Table 2. The only complication in patients with duodenal injury was a wound infection in one patient. Pyloric exclusion or duodenal diverticulization was not used for duodenal injuries in the absence of pancreatic injury. There were no late deaths, intra-abdominal abscesses, or duodenal fistulas in these patients.

There were four early deaths among the 11 patients with continued pancreaticoduodenal injuries. The remaining seven patients required repair of these wounds. Two patients with blunt grade I injuries were treated according to protocol[8] for their individual injuries. One patient with a grade I pancreatic injury developed pancreatitis. Four patients with gunshot wounds had full-thickness duodenal injuries and pancreatic injury without ductal involvement (grade II). Two of the four had primary repair of the duodenum without tube decompression; one developed an intra-abdominal abscess, the other developed pancreatitis, and both survived. The other two patients with grade II injuries had primary repair and decompression without complication. Pancreatic injuries were managed with suction drainage. One patient with a grade III injury had a defect closed that affected 30% of the duodenal circumference. Pyloric exclusion was then performed. A ductal injury was drained rather than resected owing to the patient's hemodynamic instability. Multiple intra-abdominal abscesses developed and required operative drainage. There were no septic deaths in this group of patients with combined pancreaticoduodenal injuries.

COMMENT

The indications for using various operative techniques in the management of pancreatic, duodenal, or combined pancreaticoduodenal wounds remain controversial. Stone and Fabian[4] suggested that duodenal tube decompression be used as an adjunct to suture repair for all duodenal injuries, based on a decrease of duodenal suture line dehiscence from 12% to less than 1% after changing to a policy of routine tube decompression. Vaughan et al[5] reported a 7% incidence of duodenal fistula without tube decompression and concluded that the majority of duodenal injuries could be closed without using adjunctive measures. Flint et al[6] found that duodenal fistulas did not develop when suture repair alone was used for injuries affecting less than 20% of the duodenal circumference. However, of 23 patients with wounds involving from 20% to 70% of the duodenal circumference who did not undergo decompression, seven (30%) developed leaks, and seven died. Our data indicate that injuries affecting less than 20% of the duodenal circumference can be treated safely by two-layer closure without adjunctive tube decompression and suggest that this approach is also safe for injuries affecting up to 40% of the duodenal circumference. Tube decompression should probably be reserved for injuries involving greater than 40% of the duodenal circumference, closure under tension, and associated pancreatic injury.

Heitsch et al[9] reported a 19% mortality in patients with pancreatic ductal injuries treated by drainage alone. Subsequently, a policy to use distal pancreatectomy for documented or suspected ductal injury was adopted at our institution.[7] This approach eliminated pancreas-related mortality due to distal ductal injury. A subsequent, larger study[7] showed a 3% death rate among subjects with pancreatic ductal injuries, reaffirming the value of distal pancreatectomy for pancreatic ductal injuries. Results from this study demonstrate that distal resection remains effective in reducing late septic deaths, but morbidity remains high. Drainage alone resulted in four abscesses and five fistulas in this study. The incidence of fistula formation was reduced to one in 18, after distal pancreatectomy, but intra-abdominal abscesses developed in seven of these 18 patients. This suggests that, while distal pancreatic resection does not eliminate complications, it does make them more manageable.

Our data also suggest that the pancreatic wound acts as a cofactor predisposing to the development of intra-abdominal abscess after hollow viscus injury. This is consistent with findings reported by Ivatury et al,[10] in which 58% of patients with pancreatic injury associated with colon injury experienced intra-abdominal abscess, compared with an 8% abscess rate in patients with colon injury but no pancreatic injury. Our data suggest that pancreatic injury also increases the risk of intra-abdominal abscess when the stomach and small bowel also are injured.

Several authors have liberally applied the concept of pyloric exclusion or duodenal diverticulization to the management of duodenal or proximal pancreatic injuries.[11,12] Graham et al,[12] for example, used pyloric exclusion in 74% of their cases. We believe that this approach has been overused in certain institutions, and our data suggest that complex management schemes are often unnecessary.

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Barotrauma Associated With High-Frequency Jet Ventilation for Hypoxic Salvage

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• Most reports describe reduction in proximal airway pressures with high-frequency jet ventilation. This led us to speculate that high-frequency jet ventilation might reduce barotrauma by providing alveolar ventilation at lower airway pressures. We describe a group of patients in whom a high incidence of barotrauma was observed after institution of high-frequency jet ventilation despite reduction in measured airway pressures. Fifteen hypoxic patients who could not be treated with conventional ventilation and who had no roentgenographic evidence of barotrauma were entered into the study. Airway pressures were measured during conventional ventilation and at 2 and 24 hours after high-frequency jet ventilation. Despite significant reduction in peak inspiratory and mean airway pressures, pneumothorax developed in seven of the 15 patients, an average of 21 hours after initiation of high-frequency jet ventilation. Five patients had bilateral pneumothorax and three developed tension pneumothorax. Despite reductions in proximal airway pressures, barotrauma is a significant potential complication of high-frequency jet ventilation in patients with noncompliant lungs. We currently place bilateral prophylactic thoracostomy tubes in patients with adult respiratory distress syndrome prior to initiation of high-frequency jet ventilation.

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A high mortality rate accompanies acute respiratory failure (ARF) following trauma or sepsis. Despite aggressive attempts to improve outcome since adult respiratory distress syndrome was first described by Ashbaugh and colleagues,[1] mortality still exceeds 50%.[2] Many of these deaths are not directly related to pulmonary dysfunction, but rather are inevitable consequences of multiple system organ failure.[3,4] Conversely, all surgeons caring for the critically ill know the frustration of losing patients with refractory single system pulmonary failure. In patients with hypoxia, positive end expiratory pressure has become the mainstay of treatment[5] but is frequently unsuccessful.[6,7]

One alternative to treatment with high levels of positive end expiratory pressure with standard mechanical ventilation is high-frequency jet ventilation (HFJV). Reported advantages include less circulatory embarrassment, reduced intracranial pressure in patients with head injury, reduced air leak from bronchopleural fistulae, and improved gas exchange at lower airway pressures.[8-10] It has been proposed that the reduced mean airway pressures achieved by HFJV translate into reduced pulmonary barotrauma and subsequent progression of lung injury in patients with ARF.[11-13] Close scrutiny of the literature fails to reveal clinical data to support this hypothesis. Indeed, it has been our impression that patients with poor lung compliance may experience more barotrauma with HFJV than with "conventional" ventilation (CV).

We herein describe a group of patients in which HFJV was used for hypoxic salvage. The purpose of this study was to examine the incidence of barotrauma in these patients relative to measurements in proximal airway pressure.

PATIENTS AND METHODS

Fifteen patients were switched from CV to HFJV for hypoxic salvage over a 12-month period. Eleven of the patients were male and four were female. The average age was 32 years. Ten of the patients had posttraumatic ARF (mean Injury Severity Score, 34), three patients suffered postoperative respiratory failure after elective surgical procedures, and two patients developed pneumonia during immunosuppression for renal allografts. Prior to initiation of HFJV, ventilatory support was provided by a time-cycled, volume-limited ventilator (Siemens Servo 900C, Siemens Corp, Union, NJ). Tidal volumes of 12 to 15 mL/kg were administered at an intermittent mandatory ventilation rate sufficient to maintain normocarbia and a pH above 7.35. Inspired oxygen concentration (Fio$_2$) and constant positive airway pressure (CPAP) were both manipulated to maximize oxygen delivery (Do$_2$ = [cardiac output] × [arterial oxygen content]) at the lowest possible Fio$_2$. Patients were deemed candidates for HFJV when further increases in CPAP did not produce an adequate Do$_2$ despite an Fio$_2$ of 70% or when intrapulmonary shunt exceeded 20% despite a CPAP of 15 cm of water.

High-frequency jet ventilation was provided by a jet ventilator (Healthdyne Impulse, Marietta, Ga) attached in series with a support ventilator. The jet ventilator was attached to the jet insufflation and pressure-sensing ports of a jet endotracheal tube (Mallinckrodt Critical Care, Glens Falls, NY). Gases passing through the jet insufflation port were humidified by the addition of 20 mL/h of sterile water at room temperature via a roller pump. Jet ventilation was maintained

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Table 1.—Airway Pressure Changes*

	Proximal Airway Pressure, cm H$_2$O		
	CV	**2 h After HFJV**	**24 h After HFJV**
PIP	92±6.1	41±3.3†	35±2.5†
PAW	27±2.3	15±2.2†	12±2.1†
CPAP	17±1.5	17±1.5	10±0.8†

*CV indicates conventional ventilation; HFJV, high-frequency jet ventilation; PIP, peak inspiratory pressure; PAW, mean airway pressure; and CPAP, constant positive airway pressure. The number of patients in each group was 15. Values are means ± SEMs.

†$P<.05$ vs CV within group.

Table 2.—Changes in Hypoxic Criteria*

	CV	**24 h After HFJV†**
Po$_2$, mm Hg	51±1.2	80±2.3
Do$_2$, mL/min	679±8.3	813±9.0
Qs/Qt, %	50±2.1	30±2.2
Fio$_2$	0.84±0.026	0.61±0.030

*CV indicates conventional ventilation; HFJV, high-frequency jet ventilation; Po$_2$, partial pressure of oxygen in arterial blood; Do$_2$, oxygen delivery; Qs/Qt, intrapulmonary shunt and Fio$_2$, fraction of inspired oxygen. The number of patients in each group was 15. Values are means ± SEMs.

†$P<.05$ vs CV within group.

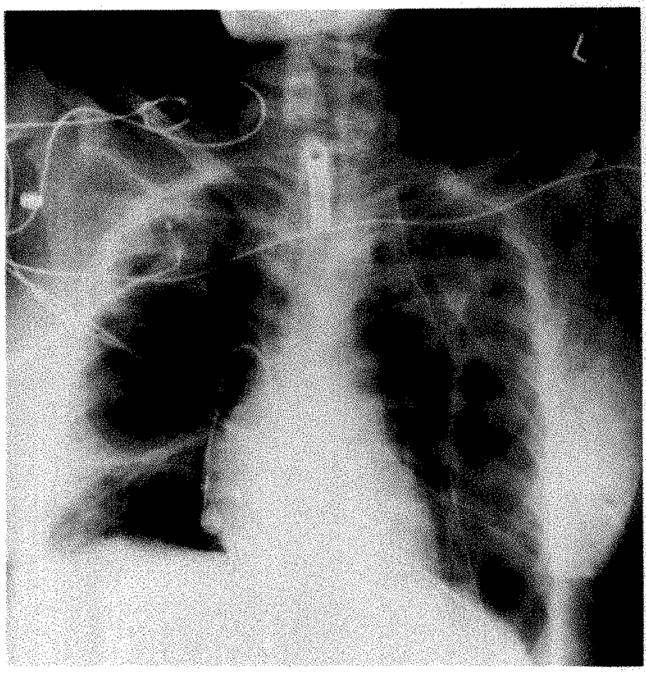

Fig 1.—Anterior chest roentgenograph of patient after weaning from high frequency jet ventilation. Note multiple bilateral pneumatoceles and the presence of three thoracostomy tubes at left.

at a frequency of 70 to 130 beats per minute, I-time of 30% to 50%, and drive pressures of 35 to 50 psi. The support ventilator was attached to the standard ventilator connection on the jet ventilator endotracheal tube and provided a continuous source of heated, humidified air of the desired Fio$_2$ for entrainment. Jet ventilations were superimposed on an intermittent mandatory ventilation of 1 to 2 beats per minute from the support ventilator. This practice of "sigh" breath application has been practiced by most physicians in an attempt to provide the high opening pressures required to achieve volume recruitment in atelectatic alveolar beds.[8]

Arterial and pulmonary artery catheters were routinely used. Arterial and mixed venous blood gas levels were analyzed using standard laboratory equipment and corrected for patient's body temperature. The thermodilution technique was used to determine cardiac output using the mean of three measurements within 10% of each other. Standard proximal airway pressures were measured during conventional ventilation. During HFJV, airway pressures were measured through the pressure-sensing port of the jet endotracheal tube, which determines pressure at the most distal aspect of the endotracheal tube.

Means and SEs were calculated for pre- and post-HFJV ventilatory variables. Differences were tested for statistical significance using a paired, two-tailed *t* test with $P<.05$ considered significant. The relationship between compliance and barotrauma was tested using Fisher's two-tailed exact test.

RESULTS

None of the 15 patients had roentgenographic evidence of barotrauma (pneumothorax, intrapleural air, or pneumomediastinum) prior to initiation of HFJV. The average Po$_2$ prior to initiation of HFJV was 51±4.5 mm Hg with an average Do$_2$ equal to 679±32 mL/min. The average Fio$_2$ prior to HFJV was 0.84±0.1. Significant decreases in peak inspiratory pressure, mean airway pressure, and required CPAP were observed at 2 and 24 hours after initiating HFJV (Table 1). Statistically significant improvements in Po$_2$, Do$_2$, and intrapulmonary shunt were brought about by jet ventilation (Table 2). Nevertheless, pneumothorax developed in seven of the 15 patients an average of 21 hours after initiation of HFJV (Fig 1). Three patients developed tension pneumothorax requiring emergency decompression, and five developed bilateral pneumothoraces. An average of four chest tubes per patient (range, two to 17) were required. The survival rate was 47% (seven of 15). One patient died as a direct consequence of tension pneumothorax. Two patients died of refractory respiratory failure, and of these, one developed hemorrhagic tracheitis (Fig 2). The remaining five deaths were in patients with multiple organ failure. Of the seven survivors, two have severe restrictive pulmonary function deficits by pulmonary function testing associated with persistent pneumatoceles (Fig 3).

Of all the pre-HFJV respiratory variables examined (Fio$_2$, CPAP, dynamic and static compliance, and minute ventilation), static compliance was the only reliable predictor of barotrauma. Mean static complicance for the entire group prior to HFJV was 14.1 mL/cm of water. The eight patients who experienced no barotrauma after initiation of HFJV had a mean compliance of 17.5 mL/cm of water compared with 10.2 mL/cm of water for those patients who suffered barotrauma. Only one patient with static compliance greater than 15 mL/cm of water suffered barotrauma (pneumothorax), while all patients with static compliance less than 15 mL/cm of water evidenced barotrauma after initiation of HFJV. The resulting relationship was statistically significant by Fisher's two-tailed exact test ($P<.001$). There was a near-equal distribution of survivors in the group with barotrauma (four survivors) and the group without (three survivors). Although this suggests no relationship of barotrauma with mortality, the sample size is not sufficient to exclude the possibility of a type II statistical error.

COMMENT

High-frequency jet ventilation is now widely employed in a number of clinical settings. It was initially developed as a technique of ventilation during operative instrumentation of the airway[14] and later became popularized for emergency airway management[15] and for bronchopleural fistula.[16] The first large clinical experience of HFJV in critically ill patients

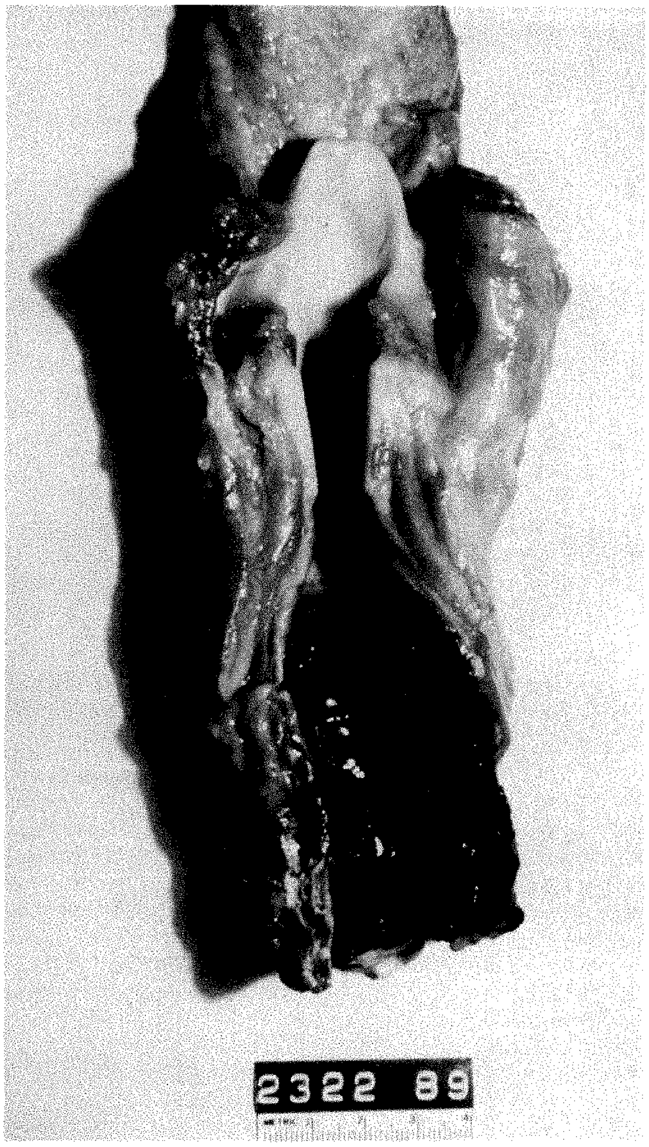

Fig 2.—Autopsy specimen of larynx and proximal trachea of patient who died following 3 weeks of high-frequency jet ventilation. Note erosion of the distal larynx and proximal trachea secondary to mandatory high cuff pressures and maximum drive pressure (50 psi).

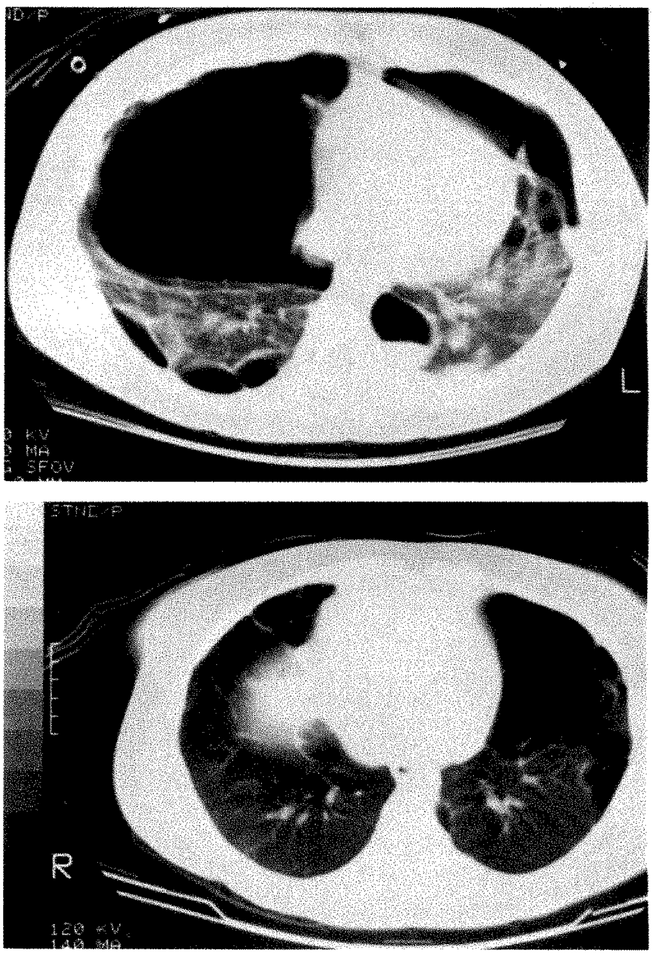

Fig 3.—Comparison computed tomographic scans of the same patient 6 (top) and 10 (bottom) months after high-frequency jet ventilation for 5 weeks. The scans represent identical levels. Note that the lungs appear to be remodeling and undergoing reexpansion.

was published in 1981 by Carlon et al.[17] The indication for HFJV in 10 of the 17 patients in their study was airway fistula. Only one patient survived of the eight patients requiring levels of CPAP over 5 cm of water prior to initiation of HFJV. This underscores the difficulty associated with application of HFJV for purely hypoxic criteria in patients with ARF.

When mechanically ventilated patients become hypoxic, application of positive airway pressure is indicated.[18,19] However, CPAP is associated with significant side effects, including increased intrathoracic pressure, reduced cardiac output,[8] increased intracranial pressure,[20] and barotrauma.[21,22] High-frequency jet ventilation is believed to reduce the risk of these complications by bringing about a decrease in proximal airway pressures. Although airway pressure reductions have been consistently measured, these theoretical advantages have been challenged. Hurst et al[23] compared HFJV and high-frequency percussive ventilation with mechanical ventilation in 54 acutely injured patients with ARF. Although reductions were reported in airway pressures, cardiac output remained unchanged after initiation of HFJV. Tabataba and Javadi[24] recently suggested HFJV as an alternative to CV during abdominal aortic operations because of decreased diaphragmatic excursions, but found no differences in hemodynamic variables between the two modes of ventilation. Clevenger et al[25] have shown that HFJV fails to selectively enhance hemodynamic performance over CV for equivalent levels of CPAP in dogs. Several studies have failed to demonstrate reductions in intracranial pressure with HFJV; however, conflicting reports can be found.[26,27]

A frequently proposed advantage of reduced proximal airway pressures brought about by HFJV is a hypothesized reduction in barotrauma.[11-13] In light of this proposed benefit, we were initially surprised by the increased incidence of barotrauma observed in the patients in our study. Several possible explanations exist for this unexpected finding. First, Simon et al[28] have demonstrated significant differences between endobronchial pressures measured at the tip of the endotracheal tube and those at the alveolar level. Sutton and Glass[29] have demonstrated significant differences in central and distal airway pressures in dogs and have further demonstrated that the proximal-to-distal pressure gradient rises after induction of lung injury with subsequent decrease in compliance. We measured proximal airway pressures and found that it is possible that pressures exerted on the distal airways and alveoli were much higher. Gallagher,[12] Hurst et al,[23] and Jonson et al[30] have independently suggested that airway pressure must be measured well below the endotracheal tube in patients undergoing HFJV to avoid underestimation. We found early in our experience with severely hypoxic patients receiving high levels of CPAP, that a 7F catheter placed through the endotracheal tube 10 cm distal to the injector, as suggested by these authors, was poorly tolerated. Furthermore, in light of the problems associated with extrapolation of proximal endobronchial pressures into pressures at the alveolar level as described by Simon et al[28] and others,[29,31] measuring pressures 10 cm distal to the endotracheal tube is unlikely to predict pressures in the distal parenchyma. This problem in interpretation of pressures may explain how pressures can build up at the alveolar level (predisposing the patient to barotrauma) with a corresponding decrease in proximal airway pressure. This phenomenon might also explain increased[32] or unaltered[33] flow through bronchopleural fistulae after initiation of HFJV despite reductions in proximal airway pressures.

Our patient population may provide a second explanation of the high incidence of barotrauma in our series compared with other reports. Because this report is limited to HFJV solely for hypoxic salvage, a marked reduction in compliance was present prior to HFJV. At the time of initiation of HFJV, our patients were profoundly hypoxic and depended on very high levels of CPAP. Our observation that barotrauma was almost certain to occur in patients with compliance less than 15 mL/cm of water and unlikely to occur in patients with higher compliance suggests that the interaction of the stiff lung with the jet ventilator is responsible for lung damage (a finding known to occur with positive pressure ventilation and in patients with lowered compliance). This speculation is supported by the two prospective comparisons of HFJV with CV that have been performed.[34,35] In both studies, patients were assigned to the protocol prior to significant alterations in pulmonary function (ie, compliance was closer to normal), and no increase in barotrauma was observed.

Since recent prospective studies have shown little or no benefit of HFJV over CV in patients with normal compliance, use of HFJV in patients with ARF will start to focus on hypoxic salvage. Our past experience with HFJV has led us to believe that this modality allows salvage of patients who would otherwise die. Our present results suggest this salvage occurs at the price of considerable barotrauma to stiff lungs. Hypoxic patients often develop diminished compliance; HFJV is not protective against barotrauma in this population and, in fact, may cause lung injury despite reductions in proximal airway pressures. Clinicians who turn to HFJV for hypoxic salvage must be wary of this frequent early complication.

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Amelioration of Cholinergic-Induced Pancreatitis With a Selective Cholecystokinin Receptor Antagonist

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• Acute edematous pancreatitis follows excessive cholinergic stimulation in patients exposed to anticholinesterase-containing insecticides. We describe the role of cholecystokinin and the benefits of cholecystokinin receptor blockade in this form of pancreatitis. A cholinergic mimetic (carbachol) was administered to rats weighing 300 to 350 g and produced a form of edematous pancreatitis that mimics that seen in humans. Animals received carbachol intraperitoneally, either alone (250 μg/kg of body weight) or with cholecystokinin-receptor antagonist devazepide (3 mg/kg of body weight) and were killed 4 hours later. Carbachol administration resulted in a 19% increase in pancreatic weight, a fourfold increase in serum amylase levels, and a 14-fold increase in serum lipase levels. Plasma cholecystokinin levels, however, were not altered. Devazepide administered prior to cholinergic hyperstimulation blocked pancreatic weight increase and reduced elevations in serum amylase levels twofold and lipase levels fourfold. Although cholecystokinin levels are not elevated in this model of pancreatitis, blockade of even low, background concentrations of this regulatory peptide is beneficial.

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Despite nearly a century of extensive clinical and experimental investigation, the cause of and early cellular events leading to the clinical manifestations of acute pancreatitis remain enigmas. Because of relative inaccessibility of the pancreas to clinical investigation, several invasive and noninvasive models of experimental pancreatitis have been described.[1] Of particular interest are models of acute edematous pancreatitis that follow the infusion of supramaximal doses of various pancreatic secretagogues.[2,3] Cholinergic hyperstimulation results in many pathologic changes in the pancreas that were originally described by Mouret[4] in 1895. Cerulein, a cholecystokinin (CCK) analogue of amphibian origin, has also been shown to induce a form of acute pancreatitis when administered in supramaximal doses.[3]

Recent experimental studies have suggested that endogenous levels of circulating CCK may play an important contributory or permissive role in non–secretagogue-dependent models of acute pancreatitis and is currently the subject of active investigation.[5] The role of endogenous CCK in promoting the pathologic effects associated with cholinergic hyperstimulation, however, is unknown. We attempted to determine the role of low, background levels of circulating CCK on the development of cholinergic-induced pancreatitis and the possible benefit of CCK receptor blockade.

MATERIALS AND METHODS

Materials included the potent and specific CCK receptor antagonist, devazepide (formerly known as MK-329 and L-364,718), dimethyl sulfoxide, aprotinin, olive oil, deoxycholic acid, carbachol, and porcine α-amylase. Amylase was measured using the Phadebas reagent (Pharmacia, Piscataway, NJ).

Male Wistar rats (National Cancer Institute, Bethesda, Md) 4 to 6 months old, weighing 300 to 350 g, were used (n = 12 in each group). All animals were fasted 18 to 24 hours before each experiment, but were allowed water. Acute edematous pancreatitis was induced by an intraperitoneal injection of carbachol (250 μg/kg of body weight or 25 μg/kg of body weight). Devazepide was administered intraperitoneally (3 mg/kg of body weight) 20 minutes prior to the administration of carbachol.[6] The vehicle for the CCK receptor antagonist, dimethyl sulfoxide, was administered intraperitoneally (0.2 mL) to the control group. Animals were killed 4 hours after secretagogue injection by rapid decapitation. Truncal blood was obtained from each animal and the whole pancreas rapidly removed and weighed. Samples of pancreatic tissue from the duodenal, gastric, and splenic lobes of the pancreas were removed and fixed overnight in 10% formaldehyde solution (buffered to pH 7.0 with 0.1-mol/L phosphate buffer) for light microscopy. Tissues were embedded in paraffin, sectioned at 5.0 μm, and stained with hematoxylin-eosin. Slides were coded and subsequently

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examined by a pathologist experienced in pancreatic pathology who was blinded to the administered drugs. Portions of pancreatic tissue 1 to 2 mm in diameter were taken from different areas and fixed with cold 2.5% acidic glutaraldehyde in 0.1-mol/L sodium cacodylate, postfixed in 1% osmium tetroxide, and embedded in epoxy resin (Epon) for transmission electron microscopy.

Blood samples were centrifuged at 1000 g for 10 minutes and plasma was decanted for subsequent enzyme assay. Amylase activity was determined by starch dye hydrolysis as described by Cseka et al[7] using Phadebas reagent. Lipase activity was assessed by its effect on oil turbidimetry as described by Vogel and Zieve.[8] Blood was collected in tubes containing ethylenediaminetetraacetic acid (5 mg/mL) and aprotinin (400 KIU/mL) and frozen at −80°C for subsequent radioimmunoassay. Samples were pooled in groups of four because of the volume required for extraction of CCK.

Plasma CCK concentrations were measured on octadecyl-silica cartridges (Sep-Pak, Millipore, Inc, Waters, Mass) by elution with 50% acetonitrile in water and 0.05% trichloroacetic acid. Following elution, samples were dried in a vacuum centrifuge to a volume of 100 to 200 µL and diluted in assay buffer for radioimmunoassay and gel permeation chromatography. Our previous experience has shown greater than 90% recovery of CCK-8 and CCK-33 added to rat plasma using this technique.[8]

Cholecystokinin concentrations were measured using an assay previously described.[9-11] The antiserum was raised to CCK-33 and recognized all molecular forms of CCK greater than the decapeptide. The tracer used was CCK-33 labeled with Bolton and Hunter reagent and purified by high-resolution, reverse-phase, high-pressure liquid chromatography.[11] There was no cross-reactivity with the gastrins or any other known hormonal peptides.[10,11] The assay measures plasma CCK concentrations in both rats and humans and can detect changes of 1 pmol/L with a 95% confidence interval.[9-11]

Results are expressed as means ± SEM. A two-tailed Student's *t* test for unpaired values was used for analysis of amylase and lipase levels and wet pancreatic weights.

RESULTS

Animals that received carbachol (250 µg/kg of body weight) alone manifested moderate forms of acute pancreatitis with fourfold increases (from 1925±225 to 7850±500 µmol/L) in serum amylase levels, 14-fold increases (from 0.8±0.5 to 11.0±1.8 IU; $P<.005$) in lipase levels, and 19% increases in wet pancreatic weight (from 311±14 to 373±12 mg/100 g of body weight; $P<.01$) (Figs 1 and 2). In addition to these pathologic effects on the pancreas, animals developed profuse lacrimation and diarrhea. Administration of higher doses of carbachol (>250 mg/kg) resulted in severe pulmonary edema and death. Pretreatment with devazepide completely blocked increases in pancreatic weight (from 311±14 to 306±15 mg/100 g of body weight) and reduced elevations of serum amylase levels from 7850±500 to 4750±380 µmol/L ($P<.005$) and serum lipase levels from 11.0±1.8 to 3.2±1.9 IU ($P<.02$).

Animals administered carbachol in doses of 25 µg/kg of body weight manifested a milder form of edematous pancreatitis and experienced ninefold elevations of lipase levels (from 9.2±2.1 to 0.8±0.5 IU, $P<.05$) and 18% increases in pancreatic weight (from 366±11 to 311±14 mg/100 g of body weight) ($P<.05$). Pretreatment with devazepide ameliorated the inflammatory response and reduced pancreatic weight (315±9 mg/100 g of body weight) ($P<0.05$) and serum lipase levels (2.2±1.5 IU/L) ($P<.05$).

Plasma CCK levels were not significantly elevated in animals administered either the higher dose (from 1.5±0.2 to 2.3±0.2 pmol/L) or the lower dose (2.4±0.7 pmol/L) of carbachol (Table). Treatment with devazepide did not alter plasma CCK levels (Table).

Light microscopy revealed that animals administered the higher doses of carbachol had marked interstitial edema and vacuolization of acinar cells compared with control animals (Fig 3). Transmission electron microscopy demonstrated a variety of changes, including multivesiculated intracellular bodies and tubule-shaped structures extensively replacing Golgi regions. Autophagic vacuoles containing flocculent, electron-dense material coexisting with myelin figures and fragments of cell debris were also noted. Similarly, many

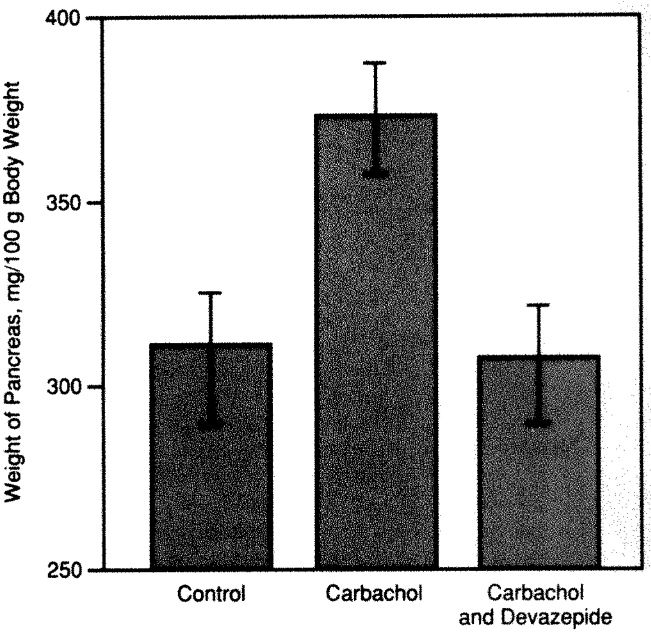

Fig 1.—Supramaximal stimulation of the pancreas with carbachol (250 µg/kg of body weight delivered subcutaneously) resulted in a mild form of edematous pancreatitis with an increase in wet pancreatic weight from 311±14 to 373±12 mg/100 g of body weight ($P<.01$). Pretreatment with devazepide (3 mg/kg of body weight) administered intraperitoneally 20 minutes prior to administration of carbachol blocked any increase in pancreatic weight (306±15 mg/100 g of body weight).

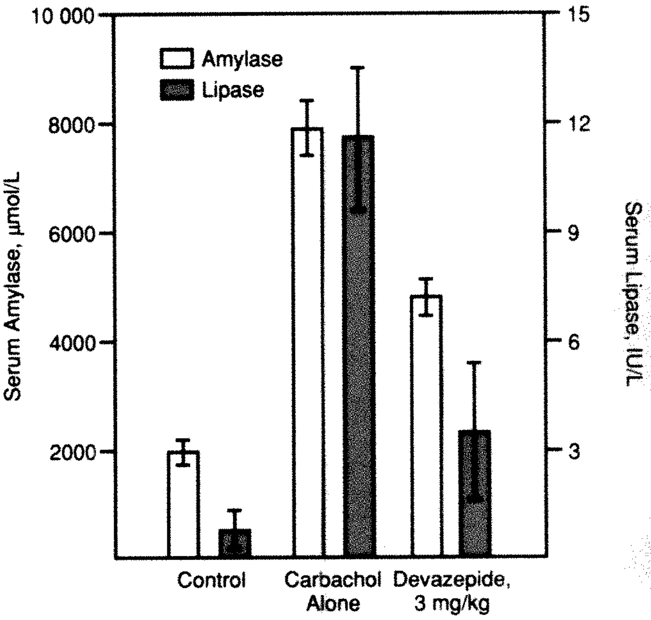

Fig 2.—Supramaximal stimulation of the pancreas with carbachol (250 µg/kg body weight) resulted in a fourfold increase in serum amylase levels and an 11-fold increase in serum lipase levels. Pretreatment with devazepide (3 mg/kg of body weight) given intraperitoneally 20 minutes prior to administration of carbachol partially blocked this response.

Plasma CCK Levels Following Cholinergic Hyperstimulation*

	CCK, pmol/L
Control	2.0
Carbachol, 250 μg/kg	1.5
Carbachol, 250 μg/kg, and devazepide	1.3
Carbachol, 25 μg/kg	2.7
Carbachol, 25 μg/kg, and devazepide	2.0

*Cholecystokinin (CCK) levels were measured by a sensitive radioimmunoassay in animals with carbachol-induced pancreatitis. Administration of devazepide (3 mg/kg) did not alter CCK levels significantly.

large vacuoles containing clumps of filamentous, electron-dense material were observed in these cells. Focally, cells with dilated cisternae of rough endoplasmic reticula containing pools of electron-dense materials were surrounded by and mixed with zymogen granules. The apical lumen and small ductules contained filamentous and membranous debris. Individual zymogen granules had marked electron-density inhomogeneity. Particularly noteworthy was a significant increase in lysosomes and lipid droplets in the carbachol-treated animals compared with the control animals. Animals administered devazepide prior to carbachol exhibited few of these changes. The only consistent ultrastructural changes noted in devazepide-treated animals were rare, autophagic vacuoles observed in a minority of acinar cells (Fig 4).

Light microscopy of samples from animals administered the lower doses of carbachol revealed features of pancreatitis similar to those of the animals administered higher doses. The abnormal expulsion of intact secretory granules into the ductules, however, was not evident. The toxic effects of pancreatitis appeared less severe than those observed after high-dose carbachol stimulation. Pretreatment with devazepide appeared to block almost all of those microscopic parameters of pancreatitis associated with cholinergic hyperstimulation.

COMMENT

Supramaximal stimulation of the exocrine pancreas results in an edematous form of acute pancreatitis. A paradoxical decrease in digestive enzyme secretion appears to accompany these pathologic changes.[1] A similar form of acute edematous pancreatitis has also been observed in humans following excessive neural (cholinergic) hyperstimulation after exposure to anticholinesterase-containing insecticides and possibly to venom from certain species of scorpions.[12,13] This phenomenon has only occurred with secretagogues that use calcium ions as intracellular second messengers of stimulus-secretion coupling.[14] The mechanism(s) responsible for these pathologic effects, however, remains unknown. The development of such noninvasive models of experimental pancreatitis has enabled further investigation of the early cellular events implicated in the development of pancreatitis. Such work has provided evidence that CCK may contribute to the development and progression of various forms of pancreatitis that are not believed to be mediated primarily via CCK receptors. Niederau et al[15] have reported that, in experimental forms of hemorrhagic pancreatitis not caused or mediated by CCK hyperstimulation, CCK receptor blockade was beneficial. This protective effect was noted when CCK receptor antagonists proglumide and benzotript were administered to young female mice with induced acute hemorrhagic pancreatitis on choline-deficient, ethionine-supplemented diets. This effect was apparent despite normal levels of circulating CCK measured by bioassay. Unfortunately, the CCK antagonists used in this study were of low potency and relatively nonspecific.

In previous studies,[16] we demonstrated that the more potent devazepide was effective in preventing the development of acute edematous pancreatitis following administration of a supramaximal dose of cerulein. In more recent studies, CCK (25 pmol/kg per hour) potentiated the severity of pancreatitis induced by bile salts or trauma.[17] Continuous blockade with devazepide improved biochemical, morphological, and survival indexes.[17]

The exact mechanism associating CCK with this form of pancreatitis is still unknown. Steer and Meldolesi[18] have reported that in both the cerulein-hyperstimulation and the choline-deficient, ethionine-supplemented diet models of pancreatitis abnormal colocalization of secretory granules and lysosomes may have important roles.[18,19] Their work suggests that a noxious stimulus (eg, massive hormonal stimulation) disrupts the intracellular transport of zymogen granules and lysosomes and may alter their membrane components. These abnormalities are believed to enable fusion of these intracellular compartments, allowing lysosomal hydrolases to prema-

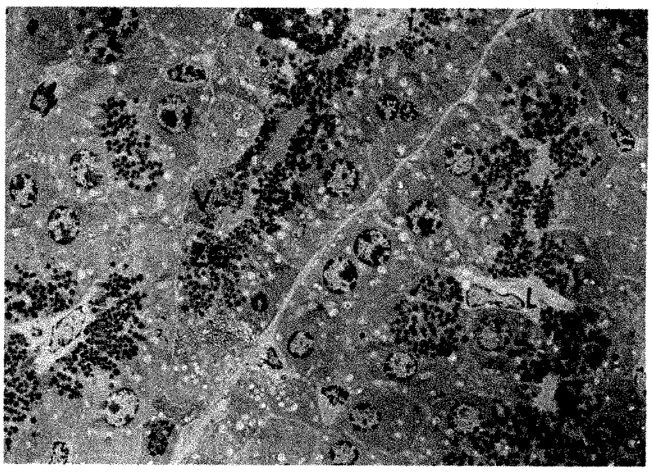

Fig 3.—Transmission electron micrograph of pancreatic tissue 4 hours after administration of the secretagogue, carbachol (250 μg/kg of body weight). Acini show apical accumulation of inhomogeneous zymogen granules (ZG) with dilatation of luminal spaces (L). Some intact zymogen granules were found in the ductules. Vacuolization (V) is evident throughout the pancreatic acinar cells (original magnification ×2000).

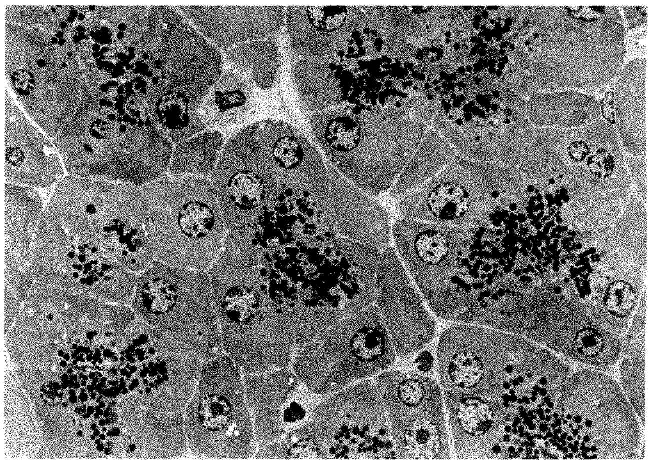

Fig 4.—Transmission electron micrograph of pancreatic tissue 4 hours after intraperitoneal administration of devazepide (3 mg/kg of body weight) followed by a supramaximal dosage of carbachol (250 μg/kg of body weight) 20 minutes later (original magnification ×1200). No histologic evidence of acute pancreatitis, as seen in Fig 3, is present.

turely activate digestive enzymes. These enzymes may cause autolysis of the acinar cell and initiate the cascade of pancreatitis.

Our results demonstrate that CCK receptor blockade with devazepide had a protective effect in a model of experimental pancreatitis that was not directly mediated via activation of CCK receptors. Devazepide prevented the development of pancreatic edema following cholinergic hyperstimulation and partially blocked the subsequent increase of amylase and lipase levels. Amylase is not solely confined to the pancreatic acinar cell; therefore, it is possible that cholinergic hyperstimulation may result in some increase in nonpancreatic sources of amylase. However, this should not affect pancreatic lipase levels. A parallel increase was noted in levels of both enzymes, suggesting that increased amylase levels were also of pancreatic origin. Devazepide does not appear to bind to pancreatic cholinergic receptors. Previous in vitro studies with dispersed acini have disclosed no alteration of carbachol-induced enzyme release.[6] We also found that carbachol-induced pancreatitis did not elevate peripheral circulating levels of CCK. Because this assay is capable of detecting 1-pmol/L alterations in plasma CCK levels and is more sensitive than previously employed assays, the possibility of any significant change in circulating levels is unlikely. It is possible, however, that local concentrations of CCK may be perturbed during this process of acute pancreatitis. Unfortunately, previous studies have not addressed this issue.

Current interpretation of locally mediated mechanisms of pancreatic secretion suggest that both CCK and cholinergic secretagogues are dependent on one another to fully stimulate exocrine secretion. It is possible that the partially protective effect of CCK receptor blockade in this model of pancreatitis reflects this interdependence of cholinergic and CCK-mediated secretagogue systems. Maximum stimulation following agonist and cell-receptor interaction may be at least partially dependent on a background or tonic level of stimulation by other endogenous secretagogues. Such a mechanism is in accordance with results from previous studies that report decreased exocrine responses to CCK in vivo after the administration of a cholinergic antagonist (eg, atropine).[20,21] A similar interdependent mechanism is thought to exist in the parietal cell, where the secretion of gastric acid is under the interactive influence of cholinergic, gastrin, and histaminergic stimuli. Blockade of either of these regulatory systems in the stomach (eg, vagotomy or antrectomy) results in decreased maximal acid output. The finding that selective CCK receptor blockade partially protects the pancreas from cholinergic hyperstimulation supports the hypothesis that a similar secretagogue-dependent mechanism may exist in pancreatic acini. Maximum stimulation of the exocrine pancreas by cholinergic stimulation, therefore, may be hindered if the background effect of CCK is blocked. These are the first results to demonstrate the beneficial effect of CCK blockade on cholinergic-hyperstimulated–induced changes in the pancreas. The ability of devazepide, or similar potent and long-acting cholecystokinin antagonists to down-regulate the pancreatic response to various stimuli may prove useful in the treatment of pancreatitis and other pancreatic disorders that are secretagogue-dependent.

The devazepide used in this study was a gift of Merck, Sharpe and Dohme (West Point, Pa). Dimethyl sulfoxide, aprotinin, olive oil, deoxycholic acid, carbachol, and porcine α-amylase were purchased from Sigma (St Louis, Mo).

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Analysis of the Transition to Percutaneous Placement of Greenfield Filters

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• To establish whether a transition from surgical to percutaneous placement of Greenfield filters was justified, a review of the safety, efficacy, and cost-effectiveness of the two approaches was conducted. Between 1984 and 1989, 168 filters were placed in 169 patients, 48 surgically and 120 percutaneously. Placement was successful in 45 (94%) of the 48 surgical patients and 120 (99%) of the 121 percutaneous patients. Filter misplacement occurred in three (6%) surgical patients and no percutaneous patients. Clinically evident femoral vein thrombosis occurred in only four (5%) of the percutaneous patients, while inferior vena cava thrombosis occurred in three (3%) of the percutaneous patients. One pulmonary embolus occurred after percutaneous filter placement and resulted in death. The cost of percutaneous placement was 58% that of surgical placement. A retrospective review of the experience in our patient population indicates that safety, cost, and ease of insertion make the percutaneous approach the procedure of choice for Greenfield filter placement.

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Despite the success of anticoagulation in preventing pulmonary embolism, there remains a group of patients who require vena caval interruption because of contraindications to anticoagulation, failure or complications of anticoagulation, or extreme risk of embolism.

Since its introduction in 1973,[1] the Greenfield vena cava filter has become widely accepted as the best currently available device for interruption of the inferior vena cava (IVC). Multiple studies have documented the safety and efficacy of the filter in preventing pulmonary embolism.[2-5]

Although the filters were originally placed surgically via internal jugular or femoral cutdown, when the technique of percutaneous placement was described in 1984[6] and 1985,[7] a number of centers embraced that technique. Several series have examined technical aspects and immediate and late complications of surgical[2-4,8-13] and percutaneous[6,7,14-19] filter placement and have found favorable results for each method. However, objective evaluation of femoral venous thrombosis following femoral percutaneous introduction has found the incidence to be as high as 30% to 40%.[17] Although of concern, the long-term clinical consequences of this finding are unknown.

In our institution, Greenfield filter placement has rapidly increased in frequency since 1984. The reasons for this marked rise in the number of filters placed include the widespread acceptance of the device, expansion of our trauma service, and an increased number of patients referred to our pulmonary group for pulmonary thromboendarterectomy. When percutaneous placement became technically feasible and appeared to be safe, there was a rapid transition from surgical placement to percutaneous placement. This study was performed to critically analyze that transition and to determine whether the change in approach has been justified. A cost comparison of the two techniques was also performed.

PATIENTS AND METHODS

The charts of all patients who had undergone placement of Greenfield vena cava filters at the University of California, San Diego, Medical Center between January 1984 and December 1989 were retrospectively reviewed. The records were specifically analyzed to determine the indications for filter placement, evidence of preexisting lower-extremity venous disease, and associated predisposing medical conditions. The majority of filters were placed prophylactically prior to pulmonary thromboendarterectomy. With regard to the procedures themselves, issues addressed included the requirement of the use of alternate insertion sites; filter misplacement or migration; hemorrhagic, thrombotic, or other early complications; and mortality and late complications. Late follow-up was obtained by clinic records or by telephone contact with patients or their physicians if they had not been seen within 6 months. In addition, the current cost of filter placement by both surgical and percutaneous approaches was determined.

Surgical placement of filters was performed as described by Greenfield et al.[20] Inferior venacavography was performed in all patients to evaluate caval size and the presence or absence of thrombus and to determine the location of the renal veins.

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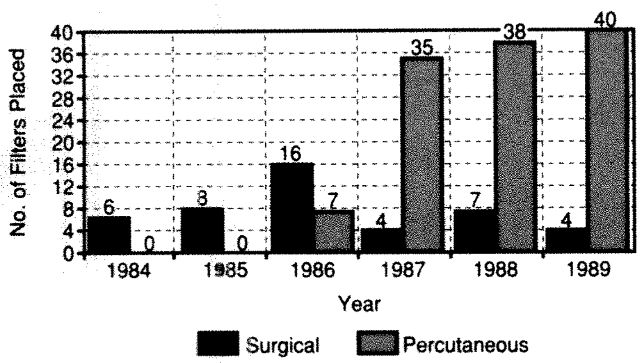

Summary of the number of Greenfield filters placed by year and the technique used from 1984 to 1989.

Table 1.—Patient Population

	No. of Patients	
	Surgical (N=48)	Percutaneous (N=121)
Age range (mean), y	19-78 (49)	15-88 (51)
Male	28	87
Female	20	34
Preexisting disease		
Trauma	6	28
Malignancy	5	7
Neurologic	0	7
Pulmonary hypertension	31	68
Other	6	11

Table 2.—Indications for Caval Interruption

	No. of Patients	
	Surgical (N=48)	Percutaneous (N=121)
Pre-PTE*	31	68
Contraindication to anticoagulant therapy	15	43
Failure of anticoagulant therapy	2	3
Prophylactic	0	7

*PTE indicates pulmonary thromboendarterectomy.

Table 3.—Approach Sites and Success Rates for Filter Placement

	Surgical*	Percutaneous*
Successful placements	45/48	120/121
Right internal jugular vein	34/39	6/8
Femoral	8/9	115/117†
Right atrium	3/6	. . .
Alternate sites	6	3

*Numbers to the left of the virgules indicate the number of successful filter placements; numbers to the right, the number of attempts with each technique at each site. Alternate sites refers to instances in which more than one site was used to accomplish filter placement.

†One patient received bilateral iliac filters.

Percutaneous filter placement requires a 24F, Coons-Amplatz sheath (Medi-tech, Watertown, Mass) to be backloaded over a 7F, 8-mm, 4-cm, angioplasty balloon catheter. When filter placement is planned, the puncture into the femoral vein is done with a "one-wall" needle to avoid inadvertent puncture of the femoral artery. The diagnostic catheter used to perform the venacavography is exchanged over a wire for the balloon catheter. The balloon catheter is placed into the proximal femoral vein, with most of the balloon being situated within the subcutaneous tissues. The balloon is then inflated to dilate the subcutaneous tissues and the entrance into the femoral vein. The balloon is deflated, and the sheath is then advanced into the femoral/proximal external iliac vein. The balloon, wire, and introducer portion of the sheath are removed, leaving the sheath in place.

The Greenfield introducer device is then placed into the sheath. The wire of the filter introducer is advanced to the appropriate level for filter placement, and the filter is advanced over the wire. When the filter-introducing capsule exits the sheath, the sheath is removed and the femoral vein is gently compressed while the filter is advanced to its appropriate infrarenal or suprarenal location. The filter is discharged, the introducer device is removed, and the femoral vein is gently compressed for 10 to 15 minutes. Steri-strips are placed across the small groin incision, a bandage is placed over the wound, and patients are returned to their rooms with instructions not to move their legs for 6 hours. Patients are observed closely by the nursing staff for the first several hours following the procedure; if bleeding occurs, another 10 to 15 minutes of gentle compression is instituted.

The right internal jugular vein has been the preferred site for surgical placement, and the right femoral vein has been the preferred site for percutaneous placement. If the right femoral vein was not available due to previous thrombosis, the left femoral vein was used. If neither femoral vein was available, the right internal jugular vein was used to place the filter either percutaneously or surgically. The position of the filter was confirmed by abdominal plain x-ray films taken after the procedure.

RESULTS

One hundred sixty-nine patients underwent placement of 168 Greenfield filters at the UCSD Medical Center between January 1984 and December 1989. As shown in the Figure, there was a transition during this period from purely surgical placement to a predominantly percutaneous approach.

Table 1 contains the demographics of the patient population receiving Greenfield filters, while the indications for filter placement are included in Table 2. Our institution is unique in that there is a collaborative effort between pulmonary medicine and cardiothoracic surgery in pioneering the treatment of pulmonary hypertension due to chronic thromboembolic disease by pulmonary thromboendarterectomy. These patients routinely have vena cava filters placed prior to surgery for their pulmonary hypertension. Patients with contraindications to anticoagulation were considered to be those with contraindications prior to initiating anticoagulant therapy and those who developed complications of anticoagulation. Failure of anticoagulation was defined as pulmonary embolism or propagation of deep venous thrombosis despite therapeutic anticoagulation. Filter placement was considered to be prophylactic when the indication was purely high risk for thromboembolism without documented deep venous thrombosis or pulmonary embolus.

Heparin was administered either subcutaneously or intravenously at the time of filter placement in 74 (61%) of 121 patients and warfarin sodium (Coumadin) was administered in eight (7%) of 121 patients; in 39 (32%) of 121 patients, no anticoagulants were administered.

Table 3 summarizes the approaches and success rates for both the surgical and percutaneous groups. Forty-five of 48 patients had filters placed successfully by a surgical approach. The right internal jugular vein was the preferred introduction site and was successful in 34 of 39 attempts, while a femoral approach was successful in eight of nine attempts. Three of six attempts at placement via the right

Table 4.—Immediate Complications of Filter Placement

Complication	No. of Patients Surgical (n=45)	 Percutaneous (n=120)
Misplacement	3	0
Hematoma/bleeding	1	7
Femoral vein thrombosis	0	3
IVC thrombosis*	0	2
Death	1	15

*IVC indicates inferior vena cava.

Table 5.—Late Follow-up After Greenfield Filter Placement

	No. of Patients Percutaneous*	 Surgical†
IVC thrombosis‡	1	1
Increased leg edema	1	0
Filter migration	0	0
Death	11	3

*Seventy-eight (74%) of 105 patients had late follow-up. The mean time to follow-up was 18 months.

†Thirty (68%) of 44 patients had late follow-up. The mean time to follow-up was 25 months.

‡IVC indicates inferior vena cava.

Table 6.—Cost Comparison (in Dollars) for Greenfield Filter Placement

	Surgical	Percutaneous
Radiology	964	1579
Filter	625	625
Operating room	1000	. . .
Anesthesia standby fee	160	. . .
Professional fee	1950	540
Total	**4699**	**2744**

atrium at the time of pulmonary thromboendarterectomy were successful. Alternate sites of insertion were required in six patients. Failed attempts were due to an inability to pass the carrier beyond the internal jugular-subclavian junction, the caval atrial junction, or the iliac vein.

In the percutaneous group, successful placement of a filter was accomplished in 120 of 121 patients, with a single patient receiving bilateral iliac vein filters. Placement was accomplished via the right internal jugular vein in six of eight patients and by femoral vein in 115 of 117 patients. Alternate sites of insertion were necessary in three instances.

Immediate complications of filter placement for the two groups are included in Table 4. Three filters were misplaced in the surgical group: two in the right renal vein from a right atrial approach and a third at the caval-atrial junction from an internal jugular approach. One filter was tilted more than 15°, and one patient developed a neck hematoma that did not require surgical drainage. One patient died within 30 days of filter placement following a pulmonary thromboendarterectomy.

There were no filter misplacements in the group undergoing percutaneous placement, although two were tilted more than 15°. Seven patients developed postprocedural hematomas or bleeding, none of which required transfusion, surgical drainage, or repair. Three patients developed clinically evident femoral vein thromboses on the side of percutaneous introduction. Of the three patients, one was receiving warfarin and one subcutaneous heparin; the third patient had been receiving heparin, which was discontinued prior to filter placement and then readministered 6 hours later.

Two patients developed an IVC thrombosis after percutaneous placement. The condition of one of these patients was diagnosed by ultrasonography and treated with a second, surgically placed suprarenal filter and anticoagulants, with the patient ultimately dying of his traumatic injuries. The second patient suffered a fatal pulmonary embolus that at autopsy appeared to originate from thrombus propagated above the filter. Neither patient had caval thrombus at the time of filter placement or evidence of femoral vein thrombosis after filter placement. Whether this represented caval thrombosis due to the filter or trapped emboli was impossible to determine. The second patient had been treated with anticoagulants after filter placement. The percutaneous approach could not be implicated as causative in either case.

Thirteen other patients in the percutaneous group died within 30 days of filter placement, six following pulmonary thromboendarterectomy and seven of complications of malignant neoplasm or trauma. Although 15 of 16 early deaths were in the group undergoing percutaneous placement, only one patient died of thromboembolic causes.

Late follow-up was achieved by telephone for 64 of 105 patients and from clinic records for 14 of 105 patients who had undergone percutaneous placement (Table 5). Forty-five (58%) of 78 patients were treated with warfarin on a long-term basis, while 33 (42%) of 78 patients were not treated with anticoagulants. One patient who received long-term warfarin therapy reported increased leg edema and discomfort in the limb in which the femoral vein had been punctured. One late instance of IVC thrombosis in a patient receiving warfarin therapy was identified by computed tomographic scan but no filter migrations were known to have occurred. Late deaths occurred in 11 patients, none of which was attributable to thromboembolic disease.

Late follow-up was achieved by telephone for 30 of 44 patients having surgically placed filters (Table 5). There were three late deaths, none of thromboembolic disease. One patient developed IVC thrombosis after discontinuing warfarin treatment and suffered a pulmonary embolus. A suprarenal filter was placed and the patient was treated with anticoagulants with resolution.

The cost of the two different approaches in our institution was also analyzed, and the data are summarized in Table 6. The cost of surgical placement is considerably higher because of a larger professional fee and the addition of operating room expenses.

COMMENT

The efficacy and safety of the Greenfield filter has been well documented.[2-5] However, there remain some questions regarding the safety of the percutaneous placement of the Greenfield filter. The major concern is femoral vein thrombosis following the percutaneous filter placement. When objective measures of femoral vein thrombosis are used, ie, duplex ultrasonography or venography, the incidence of femoral vein thrombosis is found to be as high as 30% to 40%. However, it is notable that even in those studies that have objectively identified femoral vein thrombosis, the clinical manifestations of this thrombosis are only evident in 12% of patients.[16] Long-term follow-up was obtained in 74% of the patients undergoing percutaneous filter placement to evaluate the clinical sequelae of using the femoral vein. Only three patients were noted to develop immediate clinical evidence of femoral vein thrombosis. In late follow-up, only one patient reported new or worsening leg edema. Thus, four patients (5%) undergoing percutaneous filter placement via the femoral vein had clinical findings suggestive of femoral vein thrombosis. Although the true incidence of femoral vein thrombosis may be considerably higher, the fact that the patients were not symptomatic with this relatively short period of follow-up indicates that in terms of patients' life-styles and comfort this may be a clinically insignificant problem. It is important to note that a significant number of patients in this study were receiving long-term anticoagulant therapy following pulmonary thromboendarterectomy, and the incidence of femoral vein thrombosis may be considerably less than at other institutions where the primary indication for IVC filter placement is a contraindication to anticoagulant therapy.

The incidence of caval thrombosis in the percutaneous and surgical patients who were followed up was three (3%) of 93 patients and one (3%) of 30 patients, respectively, which is comparable with that reported in surgical series.[13] The single death due to recurrent pulmonary embolus (1%) is also within the incidence found in surgical reports.[13]

Other issues that were examined included the possibility of increased hemorrhagic or infectious complications. Small postprocedural hematomas or bleeding occurred in 5% of the patients in the percutaneous group, none of whom required therapy and all of whom underwent gentle compression to control the problem. This is comparable with some surgical series reporting a 5% to 14% incidence of local hematomas[3,9] although slightly higher than other reports of a 2% incidence of hematomas with percutaneous placement. The small number of hematomas or bleeding complications following percutaneous placement was particularly gratifying in light of the fact that a large number of patients receiving filters prior to pulmonary endarterectomy had been receiving ongoing anticoagulant therapy; heparin was withheld overnight and readministered following the procedure. There were no infectious complications in the percutaneous group.

Filter misplacement and tilting was an insignificant problem in the percutaneous group; there were no misplacements and two filters (2%) were tilted more than 15°. In the surgical group there were three misplacements and one tilted filter (9%). This is similar to reports in the literature of surgical misplacement or tilting of 1.5% to 14%.[4,13,17] Both renal vein misplacements occurred during attempted filter placement from the right atrium. Although fluoroscopy was used in these cases, the lack of surgeon familiarity with the technique of filter placement was likely to have contributed to the misplacements. There were no filter migrations in either group, presumably because cavography was performed in all patients and cava size was assessed prior to filter placement.

There were no cases of femoral arterial venous fistulas following percutaneous placement, which may be because a "one-wall" needle technique was used. This theoretically allows the operator to recognize the entrance of the needle into the femoral artery prior to catheterization.

Although there were 15 deaths within 30 days of filter placement in the percutaneous group (12%), only one death was directly related to the filter, that of the patient who developed a fatal pulmonary embolus originating from thrombus propagating above the filter.

Although the right femoral vein was the preferred access for percutaneous placement, minimal problems were encountered using the left femoral vein when the right vein was not available. The percutaneous approach via the right jugular vein has been avoided since it tends to be more uncomfortable for the patient as well as awkward for the operator. The jugular approach also has the potential risk of jugular vein thrombosis,[17] pneumothorax,[16] air embolus,[17] and possible laceration of intrathoracic great veins (oral communication, J. Lyons, MD, November 1989).

Placement of the IVC filter in the radiology suite allows for venacavography to be performed and the filter to be placed during the same procedure. The excellent imaging capabilities available in radiology further aid in filter placement.

Although a prospective controlled trial comparing surgical with percutaneous Greenfield filter placement is desirable, we believe that these results demonstrating the safety, efficacy, and significant cost saving of percutaneous placement support it as the approach of choice.

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Percutaneous Catheter Drainage of Infected Pancreatic and Peripancreatic Fluid Collections

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• Operative drainage is the cornerstone of therapy for pancreatic abscess. Recently it has been suggested that successful percutaneous catheter drainage of infected pancreatic and peripancreatic fluid collections may serve as definitive therapy. We undertook therapeutic, computed tomography–directed percutaneous drainage in a selected group of 29 patients with infected pancreatic and peripancreatic fluid collections. Twenty-three patients (79%) were successfully treated with percutaneous drainage. Of six patients (21%) representing failures of percutaneous drainage, four died and two recovered after operative drainage. The four patients who died had a mean APACHE (*a*cute *p*hysiology and *c*hronic *h*ealth *e*valuation) II score of 23 and five of Ranson's prognostic signs. Ranson's signs and APACHE II scores were predictive of success and mortality. We conclude that in selected patients, infected pancreatic and peripancreatic fluid collections can be treated definitively with therapeutic percutaneous catheter drainage. Based on this experience, recommendations regarding patient selection are included.

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Over the past decade, successful percutaneous catheter drainage (PCD) of infected pancreatic and peripancreatic fluid collections has been reported,[1-5] and recently it has been suggested that PCD of pancreatic abscess may serve as definitive therapy when walled-off, liquefied collections of pus are present.[6] Infected pseudocysts and selected pancreatic abscesses have been identified as infectious complications of pancreatic inflammatory disease that are suitable for radiologic drainage. Infected pancreatic necrosis is cited as an absolute indication for open operative drainage. A selected group of patients with infected pancreatic and peripancreatic fluid collections treated with PCD form the basis of this report, which includes guidelines for patient selection. Our findings indicate that many patients with infected pancreatic and peripancreatic fluid collections can be successfully treated with PCD. Conversely, patients with infected pancreatic necrosis, including multisystem organ failure (MSOF), did not benefit from this technique.

PATIENTS AND METHODS

Twenty-nine patients with infected pancreatic and peripancreatic fluid collections were treated with PCD over a 6-year period (1982 to 1988). This group represented 1.8% of patients with a discharge diagnosis of pancreatitis at the three Medical University Hospitals (Medical University of South Carolina Hospital, Charleston; Veterans Administration Medical Center, Charleston; and Charleston Memorial Hospital). Pancreatic and peripancreatic fluid collections identified on computed tomographic (CT) scan measured at least 4 cm in diameter. Dynamic pancreatography was employed during the last 2 years of the study period. Percutaneous catheter drainage was performed in the radiology department under local anesthesia with CT, ultrasound, or fluoroscopic guidance. Needle and guidewire localization preceded placement of a 7-12F pigtail drainage catheter in the collection (Figure). All patients had a history of pancreatitis, elevated amylase levels, and bacterial or fungal organisms identified by Gram's stain and culture in the drainage fluid. Catheter drainage fluid was collected in a closed drainage system. Collections were observed weekly by CT scan or fluoroscopy. Persistent or new collections were treated with repeated PCD when needed. Causes of pancreatitis, organisms yielded by cultures, days of catheter drainage, morbidity, mortality, number of Ranson's prognostic signs, and APACHE (*a*cute *p*hysiology and *c*hronic *h*ealth *e*valuation) II severity of disease score at the time of PCD were reviewed and analyzed retrospectively. All patients received parenteral antimicrobials. Success was defined as "complete resolution of the infected collection without operative intervention." Morbidity and mortality were evaluated during the 30-day postdrainage period until eradication of the infected collection or during the period of hospitalization, whichever was longer. Ranson's prognostic signs and APACHE II score indexes were compared with success and mortality variables by means of the Kruskal-Wallis test for nonparametric data. $P<.01$ was considered significant. The data were analyzed using MacIntosh Statworks (Cricket Software, Philadelphia, Pa).

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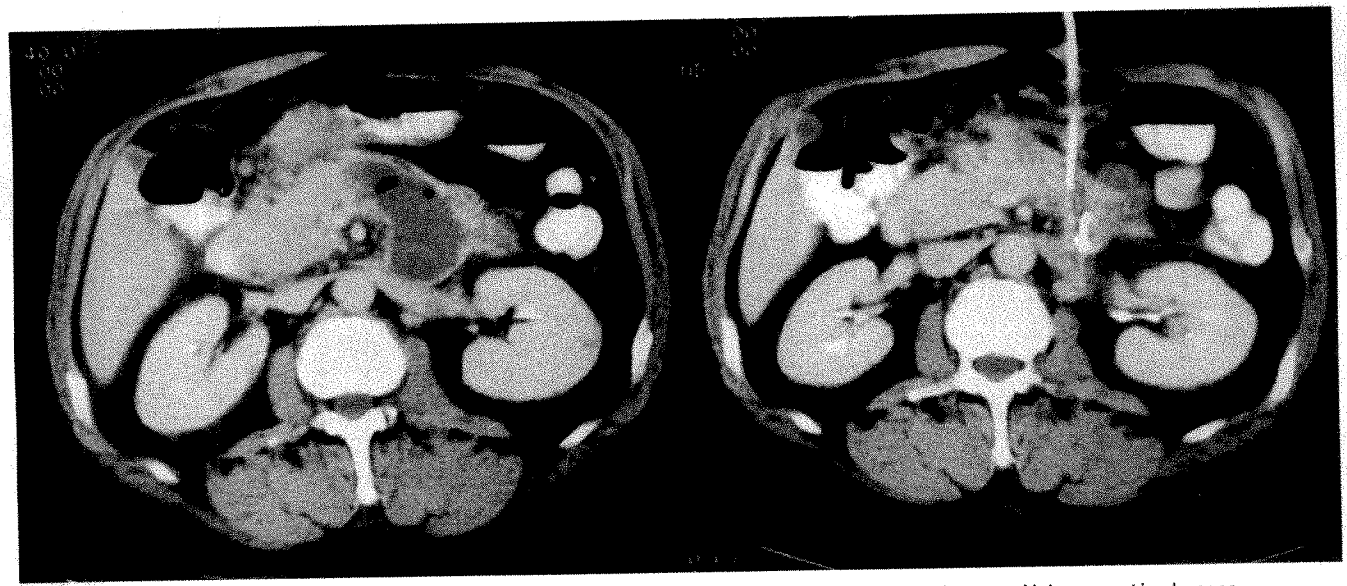

Left, Contrast-enhanced computed tomographic scan in patient with *Bacteroides fragilis* abscess. Air is present in abscess cavity in body/tail region of pancreas. Patient had one of Ranson's prognostic signs and APACHE (acute physiology and chronic health evaluation) II score of 18. Right, Computed tomographic scan following percutaneous catheter drainage. Patient required 56 days of catheter drainage and remains well at follow-up 1 year later.

RESULTS

Twenty-four men and five women with a mean age of 46 years (range, 27 to 72 years) were treated with PCD. Seventeen patients had alcohol-induced pancreatitis, three had biliary pancreatitis, one had hyperlipidemia, and one had azathioprine sodium–associated pancreatitis. Seven patients had undergone operations prior to developing infected pancreatic and peripancreatic collections; two of these developed pancreatic abscesses after vascular operations (superior mesenteric artery reconstruction, splenic/renal artery bypass), two after splenectomy for trauma, one after cholecystectomy and common bile duct exploration for biliary pancreatitis, one after laparotomy and placement of lavage drainage tubes for hemorrhagic pancreatitis, and one after pancreaticoduodenectomy for ductal adenocarcinoma.

The mean length of catheter drainage was 41 days (range, 2 to 210 days), excluding one patient who had a prolonged drainage of 600 days. Seven patients had more than one catheter used in drainage. Cultures of 20 patients yielded single organisms and nine had multiple organisms as listed below:

Organism	No. of Patients
Staphylococcus aureus	6
Pseudomonas aeruginosa	6
Candida albicans	3
Proteus mirabilis	3
Escherichia coli	2
Serratia marcescens	2
S epidermidis	2
Acinetobacter	2
Enterococcus	2
Bacteriodes fragilis	2
Klebsiella pneumoniae	1
Proteus vulgaris	1
Streptococcus pneumoniae	1
Clostridium difficile	1

Twenty-three patients (79%) were successfully treated with PCD. Of six patients (21%) representing failure with PCD, four died and two recovered after operative drainage. Four (67%) of the six patients in whom treatment failed developed infected collections after operative trauma. Twenty (91%) of 22 patients with acute pancreatitis unrelated to operative trauma were successfully treated with PCD. Patients who underwent successful drainage had a mean of two of Ranson's prognostic signs and a mean APACHE II score of 10. The mean number of Ranson's prognostic signs in patients who died was five and the mean APACHE II score was 23.

Three of the four deaths occurred in patients who had previously undergone pancreatic operations; one patient developed an infected collection following a pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas. He had MSOF that included renal and pulmonary failure, massive upper gastrointestinal hemorrhage, and a recent myocardial infarction. He died 48 hours following PDC, which was employed as a final salvage attempt.

A second patient had undergone laparotomy to place peritoneal lavage tubes for a hemorrhagic pancreatitis. He developed respiratory failure, a disseminated coagulopathy, and septic shock, and died less than 48 hours following PCD, which was employed because a second operation was considered to represent a prohibitive risk. In retrospect, this patient probably had recurrent fluid collection in association with infected pancreatic necrosis, which would not have responded to any treatment effort short of open débridement.

The third death occurred in a patient with chronic pancreatitis who underwent PCD for an infected pancreatic pseudocyst, resulting in clinical improvement and resolution of an acute recurrent attack of pancreatitis. Following 3 weeks of hyperalimentation, he underwent distal pancreatectomy, splenectomy, and lateral pancreatojejunostomy. The postoperative course was complicated by pulmonary sepsis, systemic candidiasis, and MSOF that resulted in death 3 weeks after operation. Although the response to PCD appeared to be satisfactory, the patient died during the same hospitalization, presumably from unrelated pulmonary failure and sepsis.

The final death occurred in a patient with an infected pancreatic pseudocyst that was treated with PCD because of a recent myocardial infarction. At the time of drainage, he had only three of Ranson's signs and death was attributed to cardiac failure secondary to myocardial infarction. Thus, in three of four deaths, PCD was employed in an effort to benefit a critically ill patient. Whether operative intervention could

Table 1.—Ranson's Signs and APACHE* II Scores in Patients Successfully Treated With Percutaneous Catheter Drainage and Patients Who Died

	No. of Ranson's Signs				APACHE II Scores			
	0-2	3-4	5-6	7-8	0-10	11-15	16-20	>20
No. of patients	15	10	3	1	13	6	5	5
Success	15	7	1	0	13	5	3	2
Mortality	0	2	1	1	0	0	2	2

*APACHE indicates *a*cute *p*hysiology and *c*hronic *h*ealth *e*valuation.

Table 2.—Kruskal-Wallis *K* and *P* Values Comparing Ranson's Signs and APACHE* II Score as Predictors of Success and Patient Mortality

	Ranson's Signs		APACHE II Scores	
	K	*P*	*K*	*P*
Success	10.420	.001	9.779	.002
Mortality	7.412	.006	7.077	.008

*APACHE indicates *a*cute *p*hysiology and *c*hronic *h*ealth *e*valuation.

have been successfully undertaken or would have offered the patient a better chance of survival is difficult to know.

Two patients underwent unsuccessful attempts at PCD and survived after operative drainage; both developed infected pancreatic collections after upper abdominal operations. One patient with biliary pancreatitis had percutaneous drainage of a retrogastric collection 3 weeks after undergoing cholecystectomy and common bile duct exploration. The abscess was inadequately drained and the patient required open drainage with débridement and distal pancreatectomy 48 hours after PCD. The other patient who developed an infected fluid collection in the region of the tail of the pancreas after undergoing abdominal aortic aneurysmorrhaphy with superior mesenteric artery reconstruction had a multiloculated collection with superior extension into a retrogastric location that was inaccessible to PCD. Both of these patients had resolution of sepsis after operative external drainage.

Sixteen (64%) of the 25 survivors had complications. Eleven patients developed pancreaticocutaneous fistulae, two developed pancreaticocolonic and pancreaticocutaneous fistulas, and one developed a pancreaticocolonic fistulas. All of these fistulas resolved spontaneously without operative intervention. Two additional patients developed upper gastrointestinal hemorrhage due to gastritis, not requiring transfusion.

Ranson's signs and APACHE II indexes accurately predicted success and mortality (Table 1), with Ranson's signs showing a slightly lower *P* value (Table 2). All patients with less than three of Ranson's prognostic signs or an APACHE II score less than 11 were successfully treated with PCD. Two patients with APACHE II scores greater than 20 and one patient with five of Ranson's prognostic signs also were successfully treated with PCD.

COMMENT

Improved surgical morbidity and mortality in the operative treatment of pancreatic abscess have been evident over the past decade. Mortality rates ranging from 5% to 18% have recently been reported.[7-10] The practice of wide drainage for pancreatic abscess and early operative intervention in infected pancreatic necrosis are cited as causes of improved morbidity and mortality. Dynamic pancreatography and needle aspiration of pancreatic and peripancreatic collections are noted to be helpful in the early identification of infected pancreatic necrosis.[11] There is still some difficulty, however, in labeling infected pancreatic and peripancreatic fluid collections as infected pancreatic pseudocyst, pancreatic abscess, or infected pancreatic necrosis. We have undertaken PCD of noninfected pancreatic and peripancreatic fluid collections and have previously reported a 93% success rate in eradicating pancreatic pseudocysts with PCD.[12] In the present study, infected collections were identified based on PCD drainage culture and Gram's stain. We have categorized these patients according to Ranson's prognostic signs and APACHE II score retrospectively. Although these physiologic indexes may overclassify patients into poor prognostic groups, both have proven useful in predicting outcomes in pancreatic and abdominal sepsis.[13-16] We successfully treated patients who had as many as five Ranson's signs and APACHE II scores as high as 21. The majority of patients who were successfully treated with PCD did not have severe pancreatitis, nor did they have pancreatitis related to operative trauma. Rather the presentation was one of mild to moderate pancreatitis, based on Ranson's signs and APACHE II scores.

Percutaneous catheter drainage of infected pancreatic and peripancreatic fluid collections reported by radiologists over the past decade record morbidity rates from 4% to 17% and mortality rates from 0% to 8%.[1-3,5] Variability in patient selection and the method of reporting morbidities and mortalities may account for differences in outcome reported in the surgical and the radiologic literature. Gerzof et al[17] have identified factors that are indicators of failure in percutaneous drainage of intra-abdominal abscess. These included MSOF, the presence of foreign body, hematoma, or necrotic tissue. Malangoni and associates[18] defined the "simple" intra-abdominal abscess—a unilocular cavity without evidence of enteric connection, adjacent tumor, or tissue necrosis—as best suited to PCD. Our experience with infected pancreatic collections is in accord with these conclusions. It is possible that mortality in one of our patients with MSOF may have been prevented by early surgical débridement of infected pancreatic necrosis. Pickleman and Moncada[4] postulated that PCD of a pancreatic abscess may be specifically indicated in critically ill patients as a temporizing measure, in postoperative patients with recurrent abscesses, and in patients with portal hypertension. Our data do not indicate that PCD is successful in postoperative patients with recurrent abscesses or when employed in critically ill patients as a temporizing measure.

The patients with MSOF whom we treated may have had unrecognized infected pancreatic necrosis with both a liquid and a tissue component. These patients were treated prior to the routine use of dynamic pancreatography as an adjunct in the diagnosis of pancreatic necrosis; the high number of Ranson's signs and high APACHE II scores also may indicate infected pancreatic necrosis in these patients. The critically ill patient with a high number of Ranson's signs and a high APACHE II score probably requires open operative débridement and drainage. One patient who failed PCD and required open drainage and débridement with partial pancreatectomy should have been recognized as unsuitable for percutaneous drainage.

Host-bacteria interaction is a factor responsible for the microbiologic nature of pancreatic abscess, and recently has been noted to involve predominantly gram-negative organisms.[8] The high number of *Staphylococcus* and *Candida* infections noted may be related to the number of postoperative patients treated and the use of broad-spectrum antibiotics during prolonged hospitalization in patients with severe pancreatitis. Warshaw and Gongliang[7] have reported *Staphylo-*

coccus in 36% of microbiological cultures from 45 pancreatic abscesses.

Our data suggest that in patients with infected pancreatic and peripancreatic fluid collections, PCD is most successful in the treatment of accessible, well-localized, single collections associated with a low number of Ranson's signs and low APACHE II scores. Also, in our experience PCD was not successful in critically ill patients with MSOF or in patients with recurrent postoperative abscesses. The multiple small, infected fluid collections and necrotic pancreatic and peripancreatic tissue associated with pancreatic necrosis require open operative débridement and drainage.

Based on this experience, we recommend that the following criteria be used for selecting patients for primary PCD: (1) unilocular collection, (2) absence of MSOF, (3) no evidence of pancreatic necrosis, (4) APACHE II score less than 16 and less than four of Ranson's signs. Patients who are treated with PCD as primary therapy and fail to show prompt clinical improvement should be considered for prompt operative drainage.

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Invited Commentary

Dr Adams and the coauthors of this excellent report of 29 carefully studied patients with pancreatic infection have made an important contribution to our understanding of the appropriate indications for percutaneous drainage (PCD) of pancreatic abscesses. Seven patients developed abscesses after operation and 22 had acute pancreatitis in the absence of prior operative trauma. All patients had pancreatic or peripancreatic fluid collections measuring at least 4 cm in diameter. Twenty of the 22 patients without prior operations were successfully treated by PCD. There was one death, which was presumed to be due to cardiac failure. The patient had only three of Ranson's signs. Most of the patients successfully treated were not severely ill (mean Ranson score of 2 and APACHE II score of 10).

The patients with postoperative pancreatic infection were a more heterogeneous group. Two developed pancreatic abscesses after vascular operations, two after splenectomy for trauma, one after cholecystectomy and common bile duct exploration for biliary pancreatitis, one after pancreatic cystenterostomy, and one after pancreaticoduodenectomy. Three of these patients died, and two developed MSOF and might have been better treated by operative drainage. A fourth patient had infected pancreatic necrosis and was inappropriately selected for PCD; however, this patient survived after operative débridement and drainage of infected necrosis. A fifth patient required operative drainage as the retrogastric multiloculated collection was inaccessible to PCD. The mean number of Ranson's signs in those who died was five and the mean APACHE II score was 23.

I believe the authors, based on the data presented, have correctly concluded the following:

1. Ranson's signs and APACHE II indexes accurately predicted success and mortality, with Ranson's signs showing a slightly lower *P* value.
2. Percutaneous catheter drainage is most successful in the treatment of accessible, well-loculated, single collections associated with a low number of Ranson's signs (n = 4) and an APACHE II score of less than 16.
3. Percutaneous catheter drainage is seldom successful in critically ill patients with MSOF or in patients with postoperative abscesses.
4. Multiple, small, infected fluid collections and infected necrotic pancreatic and peripancreatic tissue require operative débridement and drainage.
5. Patients treated with PCD as primary therapy who fail to show prompt improvement should, without delay, receive operative drainage.

In summary, PCD is a useful procedure in a selected group of patients who represent a small percent of patients with pancreatic infections. All such patients should be treated on the surgical service so that, in the event that PCD fails to result in improvement, movement to the operating room can be expedited.

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Chronic Alcohol Ingestion Increases Aortic Lipid Levels in Rats

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• We evaluated the effects of alcohol ingestion on aortic lipid concentrations in 15 pair-fed Sprague-Dawley rats divided into three groups of five animals each. Control rats were fed a liquid diet, with 36% of their energy provided by maltose-dextrin for 28 days, and the remaining two groups of rats were fed an equivalent proportion of their energy as alcohol for 28 days or 18 months. Alcohol-fed rats exhaled significantly greater quantities of ethane than did controls at 28 days and 18 months. Serum cholesterol levels increased by 40% and triglyceride levels increased by 80%, but phospholipid levels remained unchanged in alcohol-fed rats compared with controls. Aortic concentrations of cholesterol and phospholipids increased twofold and threefold, respectively, in alcohol-fed rats, with a corresponding alteration of the cholesterol-phospholipid ratio at both time intervals. Tissue triglyceride levels were only elevated at 28 days, and no differences in aortic lipid peroxide levels were detected between alcohol-fed rats and controls. The results of the study indicate that alcohol ingestion increases aortic cholesterol, phospholipid, and triglyceride levels at 28 days and cholesterol and phospholipid but not triglyceride levels at 18 months. The mechanisms underlying the accumulation of lipids in aortic tissue need further elucidation.

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Alcohol ingestion produces a variety of metabolic and pathologic changes in the tissues and organs of the body. The accumulation of fat within hepatocytes is believed to be a marker of alcohol-induced liver disease.[1] Although intimal fatty streaks are characteristic of the early atherosclerotic lesion, the relationship between the accumulation of lipid in the arterial wall and the ingestion of alcohol is not understood.

A number of observations have linked the use of alcohol with changes in plasma lipid levels, which may predispose to atherosclerosis. After excessive alcohol intake, elevations in plasma triglyceride, cholesterol, and phospholipid levels result in hyperlipemia.[2] Furthermore, recent studies have demonstrated that male binge drinkers have greater elevations in low-density lipoprotein cholesterol and apoprotein B levels than individuals who consume moderate amounts of alcohol regularly. A decrease in high-density lipoprotein cholesterol and apoprotein A-I levels has been observed in patients with severe alcoholic liver disease, whereas moderate drinking correlates positively with high-density lipoprotein cholesterol and apoprotein A-I concentrations.[3,4]

Alcohol use is often associated with other known risk factors for atherosclerosis, such as smoking and hypertension.[5] Recently, we demonstrated an increase in lipid peroxide levels in atherosclerotic vessels removed from patients with these risk factors.[6]

Lipid peroxidation is one mechanism by which alcohol might facilitate the uptake of lipids by tissues and organs and has been implicated in the accumulation of fat in the liver in experimental animals and humans.[7]

The association of lipid peroxidation with the accumulation of fat in the liver of alcohol-fed rats and the presence of lipid peroxides in atherosclerotic vessels led us to examine the effects of alcohol ingestion on aortic and hepatic lipids and lipid peroxides in a rat model.

MATERIALS AND METHODS

Animal Care and Treatment

Fifteen male Sprague-Dawley pair-fed rats weighing 70 to 120 g were randomly divided into three groups of five each. The animals were allowed to adjust to a liquid diet during a period of 5 days, after which control animals received a liquid diet containing 4200 J/mL, with 36% of the energy provided by maltose-dextrin. The remaining 10 animals were fed a Lieber DiCarli diet containing 4200 J/mL. Alcohol was substituted isoenergetically for maltose-dextrin and provided 36% of the energy. In both diets, 35% of the energy intake

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Table 1.—Serum Lipid Levels in Control and Alcohol-Fed Rats*

	Control	Alcohol (28 d)
Cholesterol, mmol/L	3.55 ± 1.35	4.95 ± 1.55†
Phospholipid, mmol/L	32.9 ± 9	35.2 ± 16
Triglycerides, mmol/L	0.64 ± 0.24	1.16 ± 0.48†

*Data are mean ± SD.
†$P<.05$.

Table 2.—Aortic Lipid and Lipid Peroxide Levels in Control and Alcohol-Fed Rats*

	Control	Alcohol (28 d)	Alcohol (18 mo)
No.	5	3	5
Cholesterol, mmol/L	0.05 ± 0.01	0.09 ± 0.02†	0.08 ± 0.02†
Phospholipids, mmol/L	0.9 ± 0.2	2.8 ± 1.2†	2.7 ± 0.5†
Triglycerides, mmol/L	2.0 ± 0.7	4.3 ± 1.5†	2.8 ± 0.3
Cholesterol-phospholipid ratio	0.7 ± 0.2	0.4 ± 0.1†	0.38 ± .0.1†
Lipid peroxides, fu/g × 10^{-4}	5.3 ± 2.1	5.1 ± 1.5	5.0 ± 1.7

*Data are mean ± SD. fu indicates fluorescence units.
†$P<.05$.

Table 3.—Hepatic Lipid and Lipid Peroxide Levels in Control and Alcohol-Fed Rats*

	Control	Alcohol (28 d)	Alcohol (18 mo)
No.	5	5	5
Cholesterol, mmol/L	0.11 ± 0.01	0.14 ± 0.02†	0.13 ± 0.01†
Phospholipids, mmol/L	8.6 ± 1.0	10.2 ± 0.5	9.4 ± 0.2
Cholesterol-phospholipid ratio	0.2 ± 0.0	0.2 ± 0.0	0.18 ± 0.01
Lipid peroxides, fu/g × 10^{-4}	6.5 ± 0.3	9.9 ± 1.3	14.5 ± 0.67†

*Data are mean ± SD. fu indicates fluorescence units.
†$P<.05$.

was derived from fat and 18% from protein. All of the control animals were killed at 28 days. Half of the alcohol-fed animals were killed at 28 days and the remainder at 18 months. Three hours before killing, ethane exhalation was collected noninvasively, with use of a previously described method. The aorta in each animal was excised from the arch to the bifurcation, and all fat was carefully removed from the adventitial surface. The livers and the aortas were then gently rinsed in a 0.9% sodium chloride solution to remove blood and were snap frozen at −70°C until analysis. Representative aortic and liver sections were preserved in 10% formaldehyde and stained with hematoxylin-eosin for histologic examination. All specimens were evaluated by an experienced pathologist who was "blinded" to dietary management.

Biochemical Analysis: Tissue Homogenization

Approximately 1 g of liver tissue and the entire aorta were separately homogenized in 20 and 5 mL, respectively, of a 2:1 (v:v) chloroform to methanol solution (Folch reagent).[9] The homogenates were allowed to stand at 4°C for 16 to 18 hours in sealed tubes. After 20 hours, the extracts were centrifuged for 15 minutes at 900*g*.

The tissue cholesterol content was determined on a dried aliquot of the Folch reagent extract (0.3 mL for hepatic and 0.3 mL for the aortic extract) with use of the method of Zak.[10] Triglycerides in the extract were assayed via a colorometric method described by Dole and Meinertz[11] as modified by Goldfinch and Prudhoe.[12]

Tissue phospholipid levels were determined by the method of Raheja et al[13] with dipalmitoyl phosphatidylcholine as a standard. This technique does not require the predigestion of the phospholipid for analysis. Lipid peroxide levels were determined fluorometrically on lipid extracts of aorta and liver, as described by Tappel.[14] Activation and emission wavelengths were 395 nm and 435 nm, respectively.

Data Analysis

The data are presented as the mean ± SD and were analyzed with use of Duncan's F test.

RESULTS

Ethanol-fed rats weighed significantly less than their pair-fed controls. At 28 days, control rats weighed 203 ± 11 g vs 176 ± 12 g for alcohol-fed rats. At 18 months, alcohol-fed rats weighed 273 ± 28 g compared with 480 ± 70 g for controls ($P<.05$).

Serum alcohol concentrations ranged from 0 to 95 mg/dL (median, 86 mg/dL) at the time the rats were killed.

Serum cholesterol and triglyceride levels were significantly increased in the alcohol-fed group at 28 days ($P<.05$). No differences in serum phospholipid levels were noted between control and alcohol-fed rats (Table 1).

Rats who ingested alcohol exhaled significantly greater amounts of ethane at both 28 days and 18 months compared with controls ($P<.05$). The aortas of alcohol-fed rats contained significantly greater concentrations of cholesterol, phospholipid, and triglycerides than did controls at 28 days and significantly greater cholesterol and phospholipid levels only at 18 months. The cholesterol-phospholipid ratio was significantly lower for rats fed alcohol at 28 days and 18 months compared with control animals. No significant difference in aortic tissue lipid peroxide levels was detected between controls and alcohol-fed animals (Table 2).

The livers of alcohol-fed rats contained significantly greater ($P<.05$) amounts of cholesterol than did those of controls, but the phospholipid concentrations were not different in each of the groups. In addition, concentrations of lipid peroxidation products in the liver were significantly increased in alcohol-fed rats compared with controls (Table 3).

On histologic examination, the liver specimens from the alcohol-fed rats were characterized by fatty infiltration of the hepatocytes without evidence of inflammatory infiltrates or fibrosis. No microscopic evidence of lipid deposition in the aortas of the rats fed alcohol was found.

COMMENT

The effects of alcohol on the initiation and progression of atherosclerosis continues to be debated. In 1904, Cabot[15] challenged the prevailing view that alcohol was a cause of atherosclerosis; he was able to identify atherosclerotic lesions in only 6% of alcoholic patients. In other studies of patients who died of complications of alcoholic cirrhosis, some investigators have reported an increase in coronary artery disease, whereas others have found no correlation or even a negative correlation with cirrhosis.[16,17] These conflicting results may perhaps be explained by the frequent association of alcohol with other risk factors for atherosclerosis, such as smoking and hypertension.

In our study, rats fed alcohol exhibited significant increases in serum cholesterol and triglyceride levels, whereas phospholipid levels were unaltered. Aortic cholesterol, triglyceride, and phospholipid concentrations were increased in the alcohol-fed rats at 28 days, whereas only cholesterol and phospholipid levels remained elevated at 18 months. Despite the increase in measured tissue lipid levels, however, we found no evidence of lipid deposition in the aortic intima. This discrepancy is difficult to explain but is possibly related to the magnitude or duration of cholesterol level elevation. The alterations in the cholesterol-phospholipid ratio suggest that the increase in aortic lipid levels reflects changes in the structure of the cell membranes.

Triglyceride levels were increased in the serum and aorta at 28 days and remained elevated in the aorta at 18 months. Whether this increase in triglyceride levels is due to an increase in hepatic synthesis or impaired clearance is being investigated.

When the lipid changes observed in the aorta were compared with those in the liver of alcohol-fed rats, three differences were apparent. Fatty change in the liver was obvious on both macroscopic and histologic examination, whereas such changes were not observed in the aortic walls. Hepatic cholesterol level, but not phospholipid level, was elevated, whereas both levels were elevated in the aorta. Finally, lipid peroxide levels were increased only in the liver and not in the aorta.

The mechanisms underlying alcohol-induced fat accumulation in the liver have been extensively studied.[18] These mechanisms include a reduction in fatty acid oxidation, increased lipogenesis, structural mitochondrial injury inhibiting the oxidation of two carbon fragments via the citric acid cycle, free radical–induced lipid peroxidation, and an increase in the activity of the enzymes, limiting the breakdown of phospholipids and triglycerides.[7,18]

Alcohol-fed rats demonstrated a significant increase in the amount of exhaled ethane, indicating an increase in the in vivo production of oxygen free radicals, supporting earlier reports that focused on increased lipid peroxidation in rats fed alcohol.[19,20] The increase in lipid peroxidation is probably associated with tissue damage during the metabolism of alcohol.[21-23] Ethane exhalation does not indicate the tissues or organs responsible for the generation of the free radicals. However, during alcohol metabolism, the liver is the prime organ for ethane production. As the presence of free radicals in serum and tissues are so transitory that they are difficult to measure, conjugated dienes and lipid peroxides, the more stable products of free radical–induced lipid peroxidation, are usually assayed.

While significant increases in lipid peroxide levels were noted in the liver in alcohol-fed animals at both time intervals, we were unable to identify any differences in lipid peroxide levels in aortic tissue. This was unexpected, as we had demonstrated an increase in lipid peroxide levels in atherosclerotic vessels removed from patients with multiple risk factors, including alcohol abuse. However, alcohol ingestion was associated with a decrease in the cholesterol-phospholipid ratio, a possible measure of increased membrane fluidity of aortic tissue but not hepatic tissue. These findings suggest that the mechanisms of cholesterol accumulation may differ in the liver and the aorta. The evidence of increased exhaled ethane, and lipid peroxides in the liver, suggests that free radical–induced lipid peroxidation may play a role in the accumulation of lipids in the liver. By contrast, in the aorta, a significant increase in phospholipid level, in addition to cholesterol level, and a decrease in the cholesterol-phospholipid ratio may suggest that alterations in membrane fluidity might contribute to lipid accumulation there.

Further studies are needed and are presently under way to define more clearly the mechanisms underlying this accumulation of lipid within the aorta.

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Neuropeptide Y Inhibition of Vasoactive Intestinal Polypeptide–Stimulated Ion Transport in the Rabbit Distal Colon

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• We have studied the effect of neuropeptide Y on basal and vasoactive intestinal polypeptide–stimulated changes in the short-circuit current of strips of colonic mucosa from New Zealand white rabbits mounted in Ussing chambers. When administered to the basolateral surface, neuropeptide Y is found to decrease basal short-circuit current. Neuropeptide Y inhibits vasoactive intestinal peptide–stimulated increases in short-circuit current in a concentration-dependent fashion by a tetrodotoxin-insensitive mechanism. Also, neuropeptide Y inhibited increases in short-circuit current produced by direct stimulation of adenylate cyclase with forskolin. Furthermore, neuropeptide Y prevents vasoactive intestinal peptide–stimulated increases in tissue cyclic adenosine monophosphate levels. These results indicate that neuropeptide Y administered to the basolateral membrane inhibits vasoactive intestinal peptide–stimulated short-circuit current changes by a tetrodotoxin-insensitive mechanism that decreases tissue levels of cyclic adenosine 3′,5′-monophosphate.

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Neuropeptide Y (NPY) is a 36–amino acid polypeptide that shares structural homology with pancreatic polypeptide and peptide YY.[1] It acts as a neurotransmitter in both the central and peripheral nervous system. In particular, NPY is found in high concentrations in the enteric neurons of the myenteric and submucosal ganglia.[2] Many of these neurons directly innervate the epithelial cells of the intestinal mucosa.[3,4] Subpopulations of these neurons also contain other neurotransmitters such as norepinephrine or vasoactive intestinal polypeptide (VIP).[5] It has been postulated that NPY may play a role in modulating mucosal ion transport.[6] Neuropeptide Y inhibits carbachol, VIP, substance-P, and prostaglandin E$_2$–stimulated chloride secretion in rat jejunum.[7,8] Similarly, NPY increases chloride absorption in rabbit ileum.[9] These actions of NPY may be mediated by inhibition of cyclic adenosine 3′,5′-monophosphate (cAMP) accumulation.[10] Although NPY has important effects on colonic motility,[11] the effects of NPY on ion transport by colonic epithelium are ill understood.

Vasoactive intestinal polypeptide is a 28–amino acid neurotransmitter found in the myenteric and submucosal ganglia.[12] Vasoactive intestinal polypeptide stimulates net chloride secretion in the colon,[13] activates adenylate cyclase activity, and increases intracellular levels of cAMP.[13,14] The effect of NPY on VIP-stimulated ion transport in the colon has not been studied.

The colocalization of NPY and VIP in neurons that innervate intestinal epithelia has led us to hypothesize that NPY down-regulates VIP-stimulated ion transport through direct effects on the colonic enterocytes. The specific aim of this study was to investigate the effect of NPY on VIP-stimulated ion transport in rabbit colonic mucosa and also to identify the mechanism by which NPY affects ion transport. Our studies demonstrated that NPY is a potent antagonist to VIP-stimulated ion transport and that NPY acts directly on the colonic enterocyte by a tetrodotoxin-insensitive mechanism that inhibits cAMP accumulation within these cells.

MATERIALS AND METHODS

Preparation of Colonic Mucosa

New Zealand white rabbits weighing 3 to 4 kg were anesthetized with intravenous ketamine sulfate. Segments of descending colon were harvested. The muscular layer was stripped off the submucosal layer. The specimens were mounted in lucite chambers with a surface area of 1.13 cm^2. Bathing media consisted of a Ringer's bicarbonate solution containing the following: sodium, 141 mmol/L; potassium, 5 mmol/L; calcium, 1.2 mmol/L; magnesium, 1.2 mmol/L; chloride, 122 mmol/L; bicarbonate, 25 mmol/L; potassium monobasic phosphate, 1.6 mmol/L; potassium dibasic phosphate, 0.6 mmol/L; glucose, 10 mmol/L. The bathing solutions were circulated by gas lift using 95% oxygen and 5% carbon dioxide. This solution maintains a pH of 7.4 at 37°C. The chambers and gas lifts were coated with silicone (Sigmacote, Sigma, St Louis, Mo) to minimize peptide-binding to the apparatus.

Salt-agar bridges connected the chambers to a pair of calomel electrodes for measuring the potential difference and a pair of silver–silver chloride electrodes for delivering current. During all recorded experiments, the spontaneous potential difference was countered with the use of an automatic voltage clamp (DVC 1000, World Precision Instruments, New Haven, Conn). All studies were performed using pairs of mucosal strips obtained from the same animal; one strip as a control and the other as the experimental tissue. Tissue pairs were discarded if tissue conductance varied by more than 30%.

cAMP Measurements

The following three groups were studied: (1) basal (control), no test agent added; (2) VIP (0.03 μmol/L); and (3) VIP (0.03 μmol/L) and NPY (0.03 μmol/L). Matched tissues from the same animal were used for all experimental groups. Tissue disks were sharply excised from the Ussing chambers 5 minutes after the addition of the test agents, immersed in liquid nitrogen for 30 seconds, and weighed. Cyclic adenosine monophosphate levels were determined using a protein-binding assay (Diagnostic Products Corp).[15] Results were expressed as picomoles of cAMP per gram wet weight of tissue.

Experimental Design

Two groups of experiments were performed. In the first group we tested the effect of NPY (0.003 μmol/L to 1.0 μmol/L) on basal and VIP (0.03 μmol/L)–stimulated changes in short-circuit current (Isc). We used the half effective concentration of VIP (0.03 μmol/L) as determined by previous work (G.H.B., unpublished data, 1990).

In the second group of experiments, we investigated the possible modes of action of NPY. First, the dependence of NPY (0.03 μmol/L) inhibition of basal Isc and VIP-stimulated increases of Isc on intermediary release of other neurotransmitters was tested by blocking all neuronal conductance with tetrodotoxin (1 μmol/L). Second, the ability of NPY (0.03 μmol/L) to inhibit increases of Isc produced by direct activation of adenylate cyclase with forskolin (10 μmol/L) was

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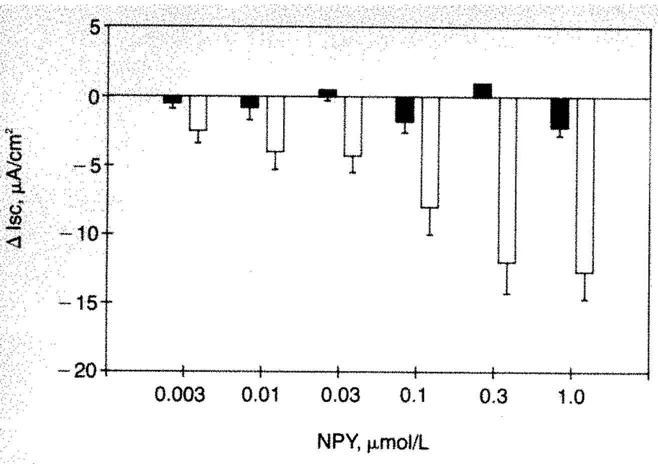

Fig 1.—Neuropeptide Y (NPY)–stimulated decrease in basal short-circuit current (Isc). Studies were performed in matched pairs of strips of rabbit mucosa mounted in Ussing chambers (n = 6 in each group). Neuropeptide Y in concentrations of 0.01, 0.3, and 1.0 μmol/L were seen to significantly ($P<.05$ by analysis of variance) decrease basal Isc. Shaded bars indicate basal Isc, and open bars, NPY alone.

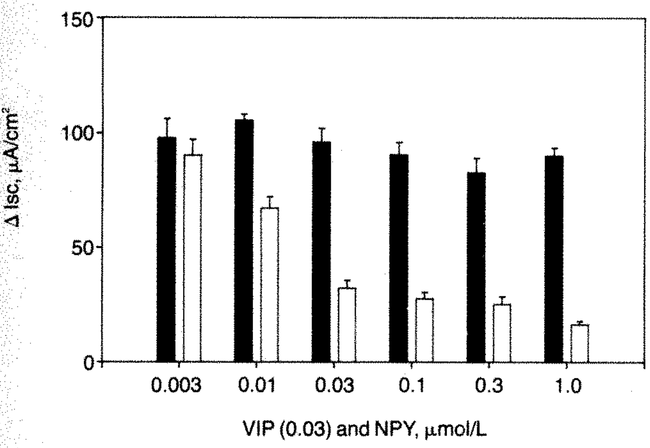

Fig 2.—Neuropeptide Y (NPY) inhibition of vasoactive intestinal polypeptide (VIP) stimulates an increase of short-circuit current (Isc). In concentrations of 0.03, 0.1, 0.3, and 1.0 μmol/L NPI significantly ($P<.05$ by analysis of variance) decreases the VIP (0.03 μmol/L)–stimulated increases of Isc. Shaded bars indicate VIP alone, and open bars, VIP and NPY.

tested. Third, the effect of NPY (0.03 μmol/L) on VIP (0.03 μmol/L)–stimulated increases of cAMP was measured. Thus, these three sets of experiments established whether NPY in this system acted through release of intermediary neurotransmitters prior to activation of adenylate cyclase or directly by attenuation of intracellular levels of cAMP.

Statistical Analysis

For electrical studies, the changes in Isc following the addition of test agents was compared with the change in the control tissues using Student's *t* test for paired samples. Changes between groups of test agents were compared by analysis of variance (ANOVA). All tests were performed using a computer software package (Systat, Evanston, Ill).

Materials

Synthetic porcine VIP and NPY were obtained from Peninsula Laboratories, Belmont, Calif; forskolin from Calbiochem, La Jolla, Calif; and tetrodotoxin and cholera toxin from Sigma, St Louis, Mo.

RESULTS

NPY Inhibition of Basal Isc

Neuropeptide Y stimulated a concentration-dependent decrease in Isc (Fig 1). The half effective concentration of NPY was 0.1 μmol/L ($P<.05$), and the maximal effective concentration, 0.3 μmol/L ($P<.01$).

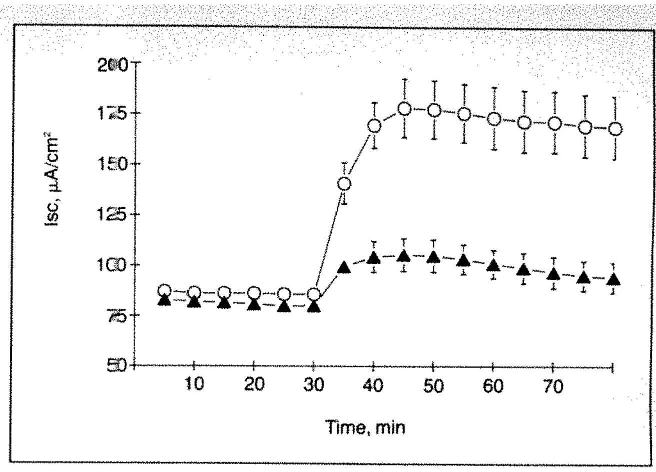

Fig 3.—Time course of vasoactive intestinal polypeptide (VIP)–stimulated (0.03 μmol/L) increase of short-circuit current (Isc) and NPY (0.03 μmol/L) inhibition of VIP (0.03 μmol/L)–stimulated increase of Isc. In both groups the agents were added to the submucosal side after 30 minutes of a stable baseline. Circles indicate VIP, and triangles, VIP and NPY.

Effects of Tetrodotoxin (10 μmol/L) on Short-Circuit Current*

Agent	Agent Alone	Agent and Tetrodotoxin
Basal	1.5 ± 1.0	−2.0 ± 1.1
NPY	−16.0 ± 4.0	−8.0 ± 1.5
VIP	77.5 ± 9.3	82.0 ± 7.3
NPY and VIP	24.5 ± 4.5	32.0 ± 4.8

*There were no significant differences ($P>.05$) between the changes of short-circuit current caused by the agents alone or in combination with tetrodotoxin. NPY indicates neuropeptide Y, and VIP, vasoactive intestinal polypeptide.

NPY Inhibition of VIP-Stimulated Isc

Neuropeptide Y significantly ($P<.01$) decreased VIP-stimulated increases of Isc in concentrations from 0.03 to 1.0 μmol/L (Fig 2). The time course of NPY (0.03 μmol/L) inhibition is shown in Fig 3. The half effective concentration of NPY for inhibition of VIP-stimulated changes in Isc was 0.03 μmol/L.

Tetrodotoxin

The effects of tetrodotoxin (1 μmol/L) on basal levels of Isc and test agent–stimulated changes of Isc are listed in the Table. The last three groups were tested in paired groups of tissues. Tetrodotoxin produced no significant ($P>.05$) effect on basal Isc or changes of Isc stimulated by VIP alone (0.03 μmol/L), NPY alone (0.03 μmol/L), or the combination of VIP (0.03 μmol/L) and NPY (0.03 μmol/L).

NPY Inhibition of Forskolin-Stimulated Increases of Isc

Forskolin (10 μmol/L) significantly ($P<.001$) increased Isc by 88.2 ± 8.7 μA/cm^2 compared with a basal change of 0.3 ± 1.1 μA/cm^2. Forskolin-stimulated increases of Isc were significantly ($P<.001$) diminished (24.5 ± 6.7 μA/cm^2 vs 88.2 ± 8.7 μmol/L) in the presence of NPY (0.03 μmol/L).

cAMP Levels

Effects of NPY on intracellular levels of cAMP are shown in Fig 4. Studies were performed in groups of three paired tissues. Vasoactive intestinal polypeptide (0.03 μmol/L) significantly ($P<.01$) increased levels of cAMP above basal lev-

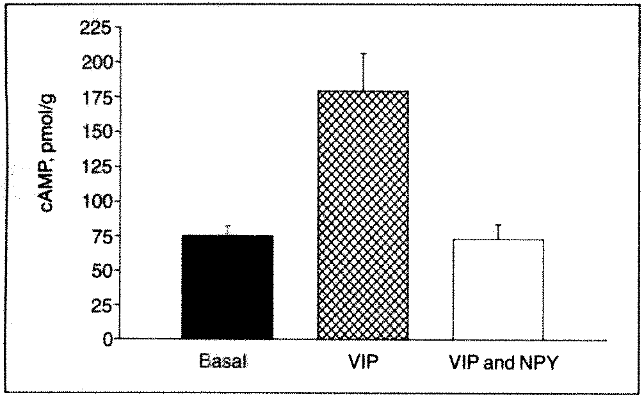

Fig 4.—Neuropeptide Y (NPY) inhibition (0.03 μmol/L) of vasoactive intestinal polypeptide (VIP) stimulates (0.03 μmol/L) increase of tissue levels of cyclic adenosine 3′,5′-monophosphate (cAMP). Studies were performed in groups of three paired tissues (n = 8). Vasoactive intestinal polypeptide was seen to significantly ($P < .01$) increase tissue levels of cAMP above basal levels. Neuropeptide Y abolishes VIP-stimulated increase of cAMP.

els. Neuropeptide Y (0.03 μmol/L) was seen to abolish VIP (0.03 μmol/L)–stimulated increases of cAMP.

COMMENT

Neuropeptide Y is found in high concentrations in the neurons of the colonic myenteric and submucosal plexuses.[2] In this study we have demonstrated that NPY decreases basal Isc of mucosal strips of rabbit colon in a concentration-dependent fashion. We have also demonstrated that NPY inhibits VIP-stimulated increases in Isc. These results suggest that NPY may play an important role in the regulation of ion transport in the colonic mucosa.

We also attempted to delineate the cellular site of action of NPY. Neuropeptide Y when added to the mucosal reservoir was found to produce no detectable change in the Isc. After a latent period, a typical response to NPY was generated from the same tissue when NPY was added to the submucosal side. This is consistent with an NPY activation site on the basolateral membrane.

Tetrodotoxin (1 μmol/L), an agent that blocks neuronal conduction, did not alter the effects of NPY on either basal Isc or VIP-stimulated increases of Isc. These results indicate that, in this system, NPY does not act by either stimulation or inhibition of the release of other neurotransmitters. This is relevant since, in some systems, NPY has been reported to act by inhibition of the release of other neurotransmitters such as VIP.[16]

Forskolin directly activates the catalytic subunit of adenylate cyclase[17] and increases intracellular levels of cAMP.[18] Forskolin (10 μmol/L)–generated increases in Isc were reduced by NPY (0.03 μmol/L) by 72%. This suggests that NPY acts in this system at a site distal to membrane receptor coupling with adenylate cyclase. These results are in contrast to other systems in which actions of NPY have been reported as mediated by a pertussis toxin–sensitive inhibitory G protein (G_i).[19-21]

Basal Isc was inhibited by NPY at a half effective concentration (0.1 μmol/L) lower than were VIP-stimulated increases of Isc (half effective concentration, 0.03 μmol/L). This suggests that the actions of NPY on basal Isc and VIP-stimulated increases of Isc are mediated by different receptors or different affinity states of the same receptor. Furthermore, NPY (0.03 μmol/L) alone did not alter basal tissue levels of cAMP. This suggests that NPY alters basal levels of Isc by a different mechanism from that mediating inhibition of VIP-stimulated increases of Isc.

Neuropeptide Y was seen to abolish VIP-stimulated augmentation of cAMP levels. This observation coupled with the ability of NPY to inhibit forskolin-stimulated increases of Isc suggests that NPY acts to inhibit VIP-stimulated increases of Isc at a site distal to the generation of cAMP. It is possible that NPY might function to increase the rate of cAMP degradation.

Neuropeptide Y and VIP are colocalized in many of the same neurons of the myenteric and submucosal plexuses.[22] In this study, we have demonstrated that NPY down-regulates the action of VIP on ion transport in the rabbit colon. Thus, NPY and VIP may participate in a coordinated regulatory mechanism that modulates colonic ion transport.

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Mortality and Quality of Life After Total Abdominal Colectomy

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• We have reviewed the results of 107 consecutive total abdominal colectomies performed at our institutions during the past 10 years. Indications for surgery were carcinoma of the colon (60), multiple polyps (nine), diverticular disease (31), and other conditions (seven). Seven (6.5%) were emergency operations. All patients had anastomosis of the terminal ileum into the lower rectum or distal sigmoid colon no more than 25 cm above the anus. Thirty days after surgery, two patients (1.8%) had died of complications of anastomotic leaks. Both were poor candidates for primary reanastomosis. Morbidity was low, occurring in 11 patients (10.3%). Follow-up evaluation of bowel function revealed satisfactory results in 102 patients (95%). Five patients (5%) had experienced chronic debilitating diarrhea. Unfavorable results were more common with diverticular disease than with neoplasia.

(*Arch Surg*. 1990;125:1564-1566)

Total abdominal colectomy (TAC) with ileorectal anastomosis has been used sparingly for many colonic diseases. The surgery is controversial because of perceived excessive mortality and increased incidence of disabling diarrhea. Dr Howard Lilienthal[1] first wrote about the functional outcome of subtotal colectomy in 1900 when he described a young patient with colitis who initially "had numerous liquid stools daily, but the number gradually diminished to where she usually had two formed stools daily." To delineate the role of TAC at the close of the same century, we review our recent experience with this operation.

PATIENTS AND METHODS

One hundred seven consecutive patients who underwent TAC from 1978 to 1988 were studied retrospectively. The ratio of men to women was 2.5:1. The mean age was 61 years (range, 30 to 87 years).

Total abdominal colectomy is defined herein as the extirpation of the colon from the ileocecal valve to a variable location extending from the level of the distal rectum to the proximal portion of the iliac colon.[2] The term *iliac colon* designates that portion of colon beginning above the rectum (S-2) that becomes the sigmoid colon at the sacral promontory. The iliac colon has no mesentery and is 6 to 8 cm long. Consequently, all anastomoses were within 25 cm of the anal verge. Specimens from all patients were pathologically examined, at which time measurements of the terminal ileum to be resected were recorded.

The indications for TAC are summarized in Table 1. Elective procedures were performed in 100 patients (93.5%). This included resections for carcinoma (59), diverticular disease as manifested by recurrent diverticulitis or bleeding (24), multiple polyps (nine), Crohn's colitis (three), and megacolon (five). Multiple lesions that either were the reason for resection or were found as a consequence of it occurred in 42 patients (Table 2). Seven patients underwent emergency operations. Six had diverticular disease, and one had complete large-bowel obstruction (Table 1).

Early in the study, colon cleansing was accomplished with cathartics and enemas and administration of oral antibiotics. More recently, cleansing for elective colectomies has been accomplished with polyethylene glycol and administration of an oral antibiotic containing neomycin sulfate and an erythromycin base. In all cases of emergency TAC, and occasionally in elective cases, perioperative intravenous antibiotics were used. Nasogastric intubation was used postoperatively in all cases until adequate bowel function returned.

Thirty-day postoperative mortality and morbidity data were available in all patients. Patients' functional status and quality of life were assessed from information obtained either by personal interviews or by mailed questionnaires. These evaluations specifically addressed the number of bowel movements per day, medications used commonly to control diarrhea, hospitalizations for dehydration, occurrence of anal incontinence, and ultimate satisfaction from the operation. Data were obtained from 93 patients (87%). Quality of life after TAC was considered excellent if the patient experienced normal bowel function without medication. Quality of life was good if the patient had one to three bowel movements per day with medication. Fair quality of life was indicated by four to six bowel movements per day with medication. Patients who experienced chronic diarrhea despite medication were considered to have poor quality of life.[3] Outcomes of colectomy were considered satisfactory only if quality of life was excellent or good.

Data were analyzed using χ^2 analysis with a protection for continuity. P values of .05 or less were considered significant.

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Read before the 14th Annual Surgical Symposium of the Association of Veterans Affairs Surgeons, Charleston, SC, May 7, 1990.

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RESULTS

The study population represents 11.6% of all operations performed for colonic diseases at our institution from 1978 to 1988. Two patients died after TAC—a mortality of 1.9%. Each patient had compounding medical problems; one had advanced cirrhosis, and the other had steroid-dependent rheumatoid arthritis. Both had protracted postoperative courses that were complicated by anastomotic leaks. Table 3 summarizes postoperative morbidity and mortality. Eleven patients sustained significant morbidity, with anastomotic leakage being the harbinger of mortality.

Patients were categorized based on the amount, in 5-cm intervals, of ileum resected. Sixty-four patients (60%) had less than 5 cm of ileum resected, 23 (21%) had 5 to 10 cm resected, two (2%) had 10 to 15 cm resected, and four (4%) had greater than 15 cm resected. In 14 patients (13%), the ileum was not resected, and these patients were excluded from analysis. Table 4 compares length of ileum resected vs functional outcome. Satisfactory results were obtained in both groups of patients with resected lengths of less than 10 cm. Among 54 patients who had less than 5 cm of ileum resected, quality of life after surgery was good to excellent in 46 patients (85%). Among 23 patients who had 5 to 10 cm of ileum resected, quality of life after surgery was good to excellent in 19 patients (83%). Poor outcome based on amount of ileum resected was not predicted.

An overall assessment of functional outcome is summarized in Table 5. Satisfactory results were achieved in 78 (84%) of the 93 patients who responded to our postoperative interviews and questionnaires. A significantly larger group of patients who underwent resection for carcinoma reported excellent quality of life compared with those who underwent resection for diverticular disease ($P<.02$). Overall, only five patients (5%) reported poor outcomes. When carcinoma and diverticular disease were compared as indications for resection, less satisfactory outcomes (fair and poor) were reported in the group with diverticular disease ($P<.07$). Since colectomy, none of these patients have required hospitalization for dehydration, and none have had incontinence.

COMMENT

High mortality and morbidity after TAC have been reported and have prohibited greater acceptance of the procedure.

Table 1.—Indications for Total Abdominal Colectomy

Diagnosis	Patients	Elective	Emergent
Carcinoma	**60**	59	1 (Obstruction)
Diverticular disease	**30**	24	4 (Bleeding) 2 (Perforation, obstruction)
Multiple polyps	**9**	9	0
Crohn's colitis	**3**	3	0
Megacolon	**5**	5	0
Total	**107**	**100** (93.5%)	**7** (6.5%)

Table 2.—Concomitant Lesions in Colectomy Specimens (N = 107)

Diagnosis	No. (%) of Patients
Synchronous carcinoma	8 (7.5)
Carcinoma and polyps	16 (15.0)
Carcinoma and villous adenoma	4 (3.7)
Multiple polyps	9 (8.4)
Diverticular disease, polyps, and carcinoma	5 (4.7)
Total	**42** (39.3)

Table 3.—Postoperative Complications (N = 107)

Complication	No. (%) of Patients	No. (%) of Deaths
Anastomotic leak	3 (2.8)	2 (1.9)
Sepsis	1 (0.9)	0
Wound infection	2 (1.9)	0
Intra-abdominal hemorrhage	2 (1.9)	0
Small-bowel obstruction	1 (0.9)	0
Pneumonia	2 (1.9)	0
Total	**11** (10.3)	**2** (1.9)

Table 4.—Length of Resected Ileum and Quality of Life After Total Abdominal Colectomy*

Length of Ileum Resected	Excellent, No. (%)	Good, No. (%)	Fair, No. (%)	Poor, No. (%)	Total, No. (%)† (N = 107)
<5 cm	32 (59)	14 (26)	6 (11)	2 (4)	**54** (50)
5 to 10 cm	13 (57)	6 (26)	2 (9)	2 (9)	**23** (21)
>10 cm	0	0	2 (100)	0	**2** (2)
Total	**45** (57)	**20** (25)	**10** (13)	**4** (5)	**79** (74)

*Mean follow-up time was 4.5 years. Percentages may not add to 100 because of rounding.

†Fourteen patients did not undergo resection, and 14 did not respond to interviews and questionnaires that assessed quality of life.

Table 5.—Diagnosis and Quality of Life After Total Abdominal Colectomy*

Diagnosis	Excellent, No. (%)	Good, No. (%)	Fair, No. (%)	Poor, No. (%)	Total, No. (%) (N = 107)
Carcinoma and polyps†	42 (70)	11 (18)	5 (8)	2 (3)	**60** (56)
Diverticular disease†	11 (41)	8 (30)	5 (19)	3 (11)	**27** (25)
Other	4 (67)	2 (33)	0	0	**6** (6)
Total	**57** (61)	**21** (23)	**10** (11)	**5** (5)	**93** (87)

*Follow-up time was 3 months to 16 years (mean, 4.5 years). Percentages may not add to 100 because of rounding.

†$P<.02$ for excellent quality of life after abdominal colectomy for carcinoma and polyps compared with colectomy for diverticular disease. $P<.07$ for fair to poor quality of life after abdominal colectomy for carcinoma and polyps compared with colectomy for diverticular disease.

Our morbidity and mortality of 10.3% and 1.9%, respectively, are not, however, unprecedented. Fry et al[4] and Bomar[5] each report a 0% mortality, and others have reported mortalities ranging from 2.4% to 14%.[2,5,6] All of these retrospective studies included a variable number of emergency procedures performed on patients of varying age, with the age differences being up to 20 years. Scott et al[3] report a combined mortality of 14%, but fully 25% of the cases were emergent, and 67% of the deaths occurred in this portion of patients. The highest mortality and morbidity figures published are 28% and 39%, respectively, reported by the Mayo Clinic.[7] In this study of 18 patients, all underwent emergency operations. Those for whom TAC was done in desperation for massive colonic bleeding had the highest mortality. Only five (28%) of the 18 patients had TAC for carcinoma. Additionally, a more recent report showed that emergency TACs in patients with obstructing left-sided carcinoma resulted in a 4.5% mortality.[8] These data are reported from a patient population for whom other operative procedures result in mortality rates of 27% and 37%.[9,10] Our study describes a large group of patients for whom TACs were performed electively and who were most suited for selective application of the procedure because most had premalignant or malignant lesions resulting from colon cancer or precancerous conditions such as multiple polyps.

A significant segment of our population had a wide variety of concomitant colonic pathologic features. The majority of these lesions were recognized preoperatively by colonoscopy. This procedure has affected our decisions to perform TAC in patients with carcinoma and polyps or multiple or large polyps and villous adenomas. Postoperative colonoscopy has also allowed us to determine the risk of developing metachronous polyps after resection for synchronous adenomatous polyps. Between 54% and 69% of patients with multiple polyps will develop additional polyps an average of 19 to 34 months after resection.[11,12] Total abdominal colectomy should be considered for patients with neoplastic colonic disease. The ultimate goal is to reduce the risk of developing carcinoma by preventing progression within the presumed polyp-carcinoma sequence.[13] Among patients with neoplastic colonic disease, the risk of developing metachronous carcinomas ranges from 1.5% to 5.1%.[5] Total abdominal colectomy should be an option in these cases, but should not be considered a prophylactic procedure without evidence of other colonic disease. Certainly, TACs should be performed for synchronous carcinomas. Additional benefits of this procedure are the simplification and low cost of the requisite survey of the colonic remnant—rigid proctoscopy or flexible sigmoidoscopy vs colonoscopy. Total abdominal colectomy should selectively be considered for patients with carcinoma of the transverse colon (to completely remove all the lymphatic drainage), familial polyposis, extensive symptomatic diverticular disease, and medically unresponsive megacolon. Additional indications for TAC may include obstructing left-sided carcinoma, granulomatous colitis, and colon carcinoma syndromes in patients less than 50 years of age.[1,2,4,5] Contraindications to this operation should include poor nutritional status, ongoing sepsis, inflammatory bowel disease involving the rectum, and clinically subnormal anal sphincter function.[6]

An emphasis has been placed on the functional outcome after TAC. With a mean follow-up of 4.5 years in 87% of our study population, we found satisfactory outcomes in 84% of patients and poor results in 5.4% of patients. The observation that a large number of bowel movements per day was not an absolute indicator of a poor result is noteworthy. Most patients experienced early postoperative diarrhea, but subsequently returned to their typical pattern of bowel habits in 6 months. These observations have been noted by others.[14] If necessary, satisfactory bowel function can be maintained with atropine sulfate and diphenoxylate hydrochloride (Lomotil), loperamide hydrochloride (Imodium), or psyllium (Metamucil).

A significantly better result was seen in those who underwent resection for carcinoma as opposed to those who underwent resection for diverticular disease. This result was also shown by Ottinger.[14] Other authors have reported equally good results. Scott et al[3] report satisfactory intestinal function in 87% of patients who underwent TAC. Lillehei and Wangensteen[2] found the incidence of diarrhea to be no higher in patients who had undergone TACs than in patients who had undergone right hemicolectomies. Bomar[5] reports a 70% satisfactory outcome in 16 patients. Ottinger[14] notes a 16% incidence of "potentially disabling diarrhea," whereas Fry et al[4] and Brief et al[6] note no disabling diarrhea. Fortunately, anal incontinence was an exceedingly rare complication in all studies.

The potential harbingers of poor functional results after TAC have been sought. Lillehei and Wangensteen[2] first proposed that the length of ileum resected best predicted outcome. Many of their patients had extensive resections of ileum, with some of the resections measuring up to 90 cm. Nearly all of their patients with resections of less than 30 cm had no diarrhea. Currently, many more conservative ileal resections are performed with TACs. In this study, 4.8% of patients had resections that exceeded 15 cm, and no correlation was found between length of ileum resected and poor outcome. The studies of Lillehei and Wangensteen[2] and Ottinger[14] both recognize that neither length of remaining rectum nor age adversely affects function outcome.

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The Influence of Renal Function on Diabetic Foot Ulceration

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• We examined the effect of renal function on the formation, severity, and outcome of diabetic foot lesions. Information was collected from a retrospective hospital chart survey and analyzed by univariate and multivariate linear regression analysis. Creatinine clearance, peripheral neuropathy, and peripheral vascular disease were all found to be independently associated with formation of foot lesions, indicating that each of these acts by distinct biologic mechanisms. Renal function had no bearing on the severity of lesions or on their eventual healing. We conclude that foot ulcers are more likely to develop in diabetic patients who also suffer from renal impairment, but they are no less likely to heal than are those in patients with normal renal function. We further conclude that attempts to preserve functional limbs in these patients are justified.

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Diabetic foot ulcers are a major public health problem in the United States, and much has been written about the physical and economic morbidity associated with them.[1,2] Renal insufficiency has long been thought to be a causative factor in the failure of these wounds to heal, based on the results of studies that examined the effects of renal impairment on experimental wound healing.[3-11] This has led to a widely held belief that major amputation may be the best treatment option for foot ulcers in diabetic patients with impaired renal function. Little critical attention, however, appears to have been focused on the actual clinical outcome of lesions in this particular group of patients. We sought to assess the influence of renal function on the development, severity, and healing capacity of diabetic foot ulcers.

PATIENTS AND METHODS

All patients examined in our study are enrolled in an integrated diabetic management program, which includes regular attendance at a diabetic foot clinic from which both outpatient and inpatient treatment is coordinated. Hospital records between 1985 and 1989 were examined, and information was collected concerning age, sex, type and duration of diabetes, smoking history, history of foot disorders, vascular status, neurologic assessment, and renal function.

Foot lesions were examined from three different viewpoints, namely, formation, severity, and eventual healing. A lesion was defined as an ulcer, an abscess cavity, or tissue necrosis. We believed that the most objective assessment of severity could be obtained by recording the type of treatment required. This approach was possible because all patients included in the study were cared for under the guidance of a single surgeon (T.J.W.) and had therefore received consistent treatment during the study period. Wounds were defined as healed when there was complete epithelial coverage.

For the purposes of our study, peripheral vascular disease was graded as being either present or absent on the basis of the patient's history (intermittent claudication or rest pain), physical examination findings (absent pedal pulses), and results of noninvasive or invasive vascular imaging, if performed. Patients with peripheral vascular disease were treated according to accepted principles. Peripheral neuropathy was assessed clinically and by electrophysiologic testing.[12] The 24-hour urinary creatinine clearance rate was used to evaluate renal function. A history of renal dialysis was also noted.

Correlations among the three aspects of ulceration studied and the other variables were examined with the use of univariate linear regression analysis. Interactions between significant variables were then examined by multivariate linear regression analysis.

RESULTS

Among a total of 281 patients who had been seen at the diabetic foot clinic, 94 had undergone a 24-hour urinary creatinine clearance evaluation during hospital admissions for foot problems or other unrelated conditions (50 women and 44 men; mean ± SD age, 57.9 ± 13.0 years). Seventy-four (78.7%) of the patients had insulin-dependent diabetes, while in 20 (21.3%), diabetes was controlled with oral hypoglycemic medication. The mean (± SD) duration of diabetes was 11.0 ± 10.2 years. The mean creatinine clearance rate for the whole patient group was 64.6 ± 29.9 mL/min. Three patients were being treated with hemodialysis.

Lesion Formation

Forty-five (47.9%) of the 94 patients developed a total of 105 foot lesions during the average follow-up period of 34.9

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Table 1.—Correlation of Lesion Formation by Univariate and Multivariate Analysis*

	Univariate Analysis	Two-Term Analysis	Three-Term Analysis
Albumin	<.001	<.05	. . .
Duration of diabetes	<.001	NS	. . .
Peripheral neuropathy	<.001	<.001	<.001
Creatinine clearance	<.001	. . .	<.001
Peripheral vascular disease	<.05	. . .	<.001

*Values represent *P* values. NS indicates not significant.

Table 2.—Relationship of Creatinine Clearance, Peripheral Neuropathy, and Peripheral Vascular Disease (PVD) to Treatment Required

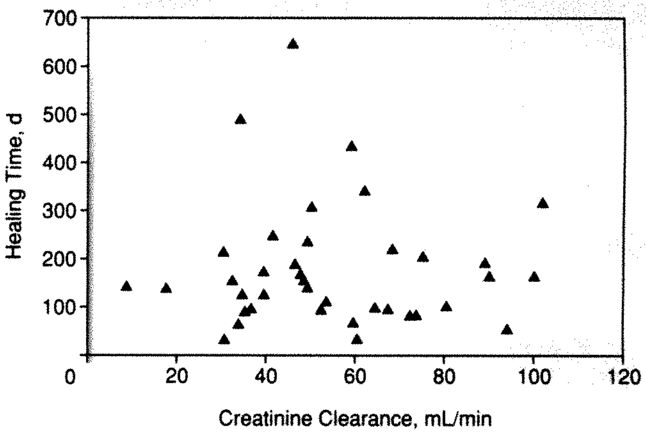
	Treatment Group			
	No Lesions (n=49)	Débridement (n=24)	Partial Amputation (n=16)	Major Amputation (n=5)
Mean ± SD creatinine clearance, mL/min	74.0±32.1	55.2±25.6	50.8±23.1	61.2±19.2
Prevalence of neuropathy, %	29	86	94	75
Prevalence of PVD, %	22	36	24	60

months (range, 6 to 80 months). Thirty-nine (87%) of the 45 patients with foot lesions developed a total of 87 ulcers/abscesses that were believed to be primarily neuropathic, based on the clinical history and physical examination. The remaining six patients (13%) developed a total of 18 lesions that were believed to be primarily ischemic, again based on the clinical findings.

Correlations were sought between lesion formation and the variables mentioned above with use of univariate linear regression analysis. The variables that were found to show significant correlations were then compared with use of multivariate analysis (Table 1). Lesion formation correlated with each of the variables shown in Table 1 when tested individually. Albumin level, duration of diabetes, peripheral neuropathy, and creatinine clearance were most significantly associated with lesion formation, while peripheral vascular disease had a weaker (but still significant) association. No correlations were noted between age, sex, type of diabetes, or smoking history and lesion formation. In the two-term analysis, albumin level and duration of diabetes both showed less correlation with lesion formation when the presence of peripheral neuropathy was considered. The three-term analysis, however, showed that peripheral neuropathy, creatinine clearance rate, and peripheral vascular disease each maintained their individual correlations with lesion formation when analyzed together.

Lesion Severity

Patients were divided into three groups based on the treatment of their lesions. The first group required only débridement of the lesions, the second required toe or partial foot amputation, and the third required major amputation. In cases where patients had more than one lesion and thus required different treatments, the most severe outcome was used in the analysis.



Healing times of diabetic foot ulcers related to creatinine clearance.

The mean creatinine clearance rates for each of these three groups are shown in Table 2. No significant differences were detected among the mean creatinine clearance rates of each group. The prevalence of peripheral neuropathy was not statistically different among the groups, but there was an increased incidence of peripheral vascular disease in the five patients who required major amputation.

Time to Healing

Among the 45 patients with lesions, five required major amputation; these patients were excluded from the analysis of healing time. Thirty of the remaining 40 patients have healed lesions. The mean (±SD) healing time was 159±98 days. No correlation was detected between wound healing time and creatinine clearance with the use of linear regression analysis and the rank sum test (Figure). The same tests revealed no correlation of peripheral neuropathy and peripheral vascular disease with healing time. Ten patients currently have unhealed lesions, but their creatinine clearance rates were no different from those whose lesions have healed (49.7±26.9 mL/min vs 50.1±21.3 mL/min, $P>.05$). One of these 10 patients is receiving hemodialysis; of the other two patients receiving dialysis, one had never had a foot lesion and the other had a history of two lesions, both of which healed satisfactorily.

COMMENT

We examined how renal function is related to the formation, severity, and outcome of diabetic foot ulcers. The possibility that impaired renal function may affect wound healing was first raised during the Korean War.[13,14] Experimental work has since examined the effects of uremia on wound healing in animals and in humans.[8-11] Although a number of these studies have demonstrated biochemical defects and decreased wound strength in diabetes and renal insufficiency, none has shown that clinical wound closure per se is impaired. Such data would be important in the selection of a course of management for patients with diabetic foot ulcers, as wound closure is the most important step in reducing the probability of limb-threatening infections.

Our data indicate that renal insufficiency, peripheral neuropathy, and peripheral vascular disease are each independently associated with ulcer formation, suggesting that different biologic mechanisms are operating in each case. The associations found between albumin level and lesion formation and between the duration of diabetes and lesion formation were secondary to the correlation of peripheral neuropathy with these two variables.

The mechanisms by which neuropathy and peripheral vascular disease lead to ulcer formation are readily apparent. Neuropathy results in an abnormal distribution of weight with high-pressure zones that produce trauma via excessive static and dynamic forces.[15] Peripheral vascular disease causes reduced extremity blood flow, thereby impairing the supply of nutrients available for tissue healing.

The mechanism by which renal insufficiency contributes to the formation of diabetic foot ulcers is not as readily apparent. Ulcers most frequently develop following trauma to subcutaneous tissues beneath a callus. The tissue trauma leads to hematoma and cavity formation. Ulcers ultimately appear when these cavities communicate with the exterior via a defect in the callus.[16] Under physiologic conditions, a balance exists between the destructive processes and the early inflammatory response, which initiates wound healing processes. Several responses that are important in the early phase of wound healing have been shown to be deficient in renal insufficiency and in diabetes. Impaired leukocyte function has been documented in diabetes[17] and in renal function impairment. Reduced neutrophil adherence has also been reported in both conditions,[11] and impaired phagocytosis and chemotaxis have been associated with diabetes.[18,19] Wound collagen production[6] and immunologic responses to lymph-borne tissue antigens[20] have been shown to be impaired in uremia. These abnormalities may be compounded in the presence of both renal impairment and diabetes, impairing the initial response to trauma in such a way that ulcers develop in circumstances that would normally resolve without skin breakdown. The mechanisms by which renal impairment produces these effects are unclear, but increased systemic levels of metabolic wastes (eg, urea) may have adverse cellular effects of this nature.

Statistical analysis suggests that the process of initial ulcer formation is different from that which determines ulcer severity and eventual healing. These latter two variables bear no correlation to the degree of renal function or to the presence of peripheral neuropathy or peripheral vascular disease. The absence of a correlation between peripheral vascular disease and ulcer healing time can be explained by the fact that arterial reconstruction was performed if ischemia were expected to delay healing. Peripheral neuropathy would not be expected to correlate with healing time, as most of the lesions in this study were believed to be neuropathic. The fact that renal impairment correlates with lesion formation but not with healing time may be explained by postulating an effect on the early inflammatory response to trauma but not on the later stages of wound healing, namely, epithelialization and wound contraction. It is also possible that wound healing is less impaired in an open, débrided wound compared with the closed cavities that are characteristic of ulcer formation.

The implications of these findings are important in the care of diabetic patients with or without foot lesions. Patients with impaired renal function are at a higher risk of developing foot lesions and thus need intensive surveillance and careful preventive care, particularly if they also have peripheral neuropathy or peripheral vascular disease. The correlation between decreasing creatinine clearance rate and increasing ulcer formation is linear. Thus, patients with the lowest creatinine clearance rates are at highest risk. Once a lesion develops, however, individuals with impaired renal function can expect their lesions to be no more severe than those in patients with normal renal function. They may also expect an acceptable chance of healing, given adequate treatment. Therefore, it is the policy of our unit to monitor these patients regularly in an attempt to prevent ulcer development. However, if an ulcer does develop in a diabetic patient with impaired renal function, our goal is to obtain wound healing and foot salvage through complete débridement while preserving all healthy functional tissue.

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Does Somatostatin Analogue Prevent Experimental Acute Pancreatitis?

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• Because somatostatin is a potent inhibitor of pancreatic secretion, we hypothesized that pretreatment with somatostatin analogue octreotide (SMS 201-995) might prevent cerulein-induced edematous pancreatitis. We studied 18 rats prepared with jugular vein catheters. The following agents were administered intravenously to groups of four rats for 6 hours: 1 mL/h (control) crystalloid solution; 1-μg/kg bolus then 1 μg/kg per hour of octreotide; and 5 μg/kg per hour of cerulein; also, in a fourth group of six rats, octreotide and cerulein were administered simultaneously. At the end of experiments, blood was drawn for plasma amylase determinations; rats were killed and pancreata were examined. Supramaximal cerulein administration to conscious rats induced hyperamylasemia and edematous pancreatitis, confirming previous observations; in both groups of rats receiving cerulein, there was prominent interstitial edema, acinar vacuolization, and mild-to-moderate acute inflammation. While octreotide pretreatment of rats with cerulein-induced acute pancreatitis was associated with a lesser increase of wet pancreas weight and plasma amylase concentration, there was little overall benefit of octreotide pretreatment in this form of experimental acute pancreatitis.

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Acute pancreatitis is a common clinical problem, but treatment remains nonspecific and primarily supportive. Effective therapy should favorably alter the natural history of the disease, ultimately decreasing associated morbidity and mortality. The suppression of pancreatic exocrine function has long been accepted as a cornerstone in the treatment of acute pancreatitis because pancreatic stimulation by food in the patient recovering from acute pancreatitis often causes an acute exacerbation of the disease.

Somatostatin is an endogenous cyclic tetradecapeptide that has numerous inhibitory actions on gastrointestinal function; in particular, it suppresses pancreatic exocrine and endocrine secretion.[1-3] Somatostatin has been shown to have a beneficial effect in several models of experimental acute pancreatitis.[4,5] Octreotide (SMS 201-995, Sandostatin, Sandoz, East Hanover, NJ) is a longer-acting octapeptide, similar to native somatostatin, that inhibits spontaneous and stimulated pancreatic secretion.[6-8]

Administration of supramaximal doses of the pancreatic secretagogue cerulein causes hyperamylasemia and acute edematous pancreatitis in rats, which is associated with gross and ultrastructural changes.[9-12] In addition, cerulein-induced acute pancreatitis causes marked impairment of pancreatic exocrine function.[12,13] We have studied this experimental preparation of acute pancreatitis and found it to be a useful and reproducible model. We hypothesized that octreotide might ameliorate or prevent acute pancreatitis induced by supramaximal cerulein administration.

MATERIALS AND METHODS

Eighteen Sprague-Dawley rats weighing 300 to 350 g were prepared. General anesthesia was induced with 5 mg/kg of intraperitoneal acepromazine maleate and 50 mg/kg of ketamine hydrochloride. A jugular vein Silastic catheter was inserted, through which 5% dextrose and 0.45 mmol/L sodium chloride with 20-mEq/L potassium chloride was continuously administered to all rats at 1 mL/h using a syringe pump (Sage Instruments, Cambridge, Mass). Anesthetized rats were placed prone in restraining cages. When the rats awakened, standard food and water were made available ad libitum.

On the first postoperative day, the rats were divided into four groups for the experiments. Group 1 rats (n = 4) were administered crystalloid solution intravenously (1 mL/h) as a control. Group 2 rats (n = 4) were treated with octreotide intravenously, first a 1-μg/kg bolus, then 1 μg/kg per hour for 6 hours. Group 3 rats (n = 4) were given 5 μg/kg per hour of cerulein (Sigma Chemical Co, St Louis, Mo) intravenously for 6 hours. Group 4 rats (n = 6) received a 1-μg/kg intravenous bolus of octreotide followed by a simultaneous infusion of 1 μg/kg per hour of octreotide and 5 μg/kg per hour of cerulein for 6 hours. At the completion of experiments, blood was drawn to measure plasma amylase concentration (ACA III, Du Pont, Wilmington, Del); results are reported in units per liter. Then, each rat was anesthetized with intravenous ketamine and acepromazine and killed with intravenous potassium chloride. The pancreas was excised in standard fashion and weighed. Each pancreas was fixed in 10% formaldehyde solution. In blind fashion, hematoxylin-eosin–stained sections of each pancreas were examined microscopically for interstitial edema, granulocyte infiltration, acinar vacuolization, and cell necrosis, as described previously.[14] Results of plasma amylase concentration and wet pancreas weight were analyzed by Bonferroni analysis of variance and differences were considered significant at $P < .05$.

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RESULTS

There was no morbidity associated with housing rats in Bollman cages for 24 hours following surgical preparation and during the 6-hour experiments. The rats consumed food and water liberally, and urinated and defecated frequently for the duration of the experiments.

Plasma amylase concentration was determined in all rats at the conclusion of experiments. Mean plasma amylase concentration is presented in the Table. The administration of cerulein with or without octreotide resulted in markedly increased mean plasma amylase concentration above values for rats treated with crystalloid (group 1) and octreotide alone (group 2). Comparing the two cerulein-treated groups (groups 3 and 4), the mean plasma amylase concentration was not found to be significantly greater in group 3 rats, which received only cerulein. A comparison of wet pancreas weight is also presented in the Table. Wet pancreas weight was not significantly increased in the two groups receiving cerulein; it was highest in the group receiving only cerulein (group 3).

Plasma Amylase and Wet Pancreas Weight*

Rat Group (n)	Plasma Amylase, U/L	Wet Pancreas Weight, mg
1 (4)	1460 ± 90	276 ± 17
2 (4)	970 ± 130	255 ± 20
3 (4)	25 700 ± 3200†	471 ± 97
4 (6)	16 400 ± 2130†	334 ± 27

*Rat groups were administered the following agents intravenously: group 1, crystalloid solution; group 2, somatostatin analogue SMS 201 995; group 3, cerulein; and group 4, SMS 201 995 and cerulein. Values are mean ± SEM.

†Significant difference from group 1 and 2 values, $P < .05$.

Under light microscopy, pancreata from rats receiving crystalloid or octreotide alone appeared normal (Fig 1). In both rat groups receiving cerulein, alone or with octreotide, pancreas specimens were histologically similar. There was microscopically prominent interstitial edema (Fig 2) and acinar vacuolization (Fig 3) as well as mild-to-moderate acute inflammation, especially in periductal regions (Fig 4). Mild granulocyte infiltration was noted in the pancreatic acinar parenchyma. On gross inspection of the abdominal cavity in rats treated with cerulein, peripancreatic fat necrosis was frequently observed (groups 3 and 4). No hemorrhage was seen.

COMMENT

Experimental acute pancreatitis was induced by supramaximal administration of cerulein, thus confirming our previous observations.[12,13] The morphologic changes and hyperamylasemia that we observed in these experiments are consistent with those reported by other investigators.[9-11] The observations reported herein demonstrate the reproducibili-

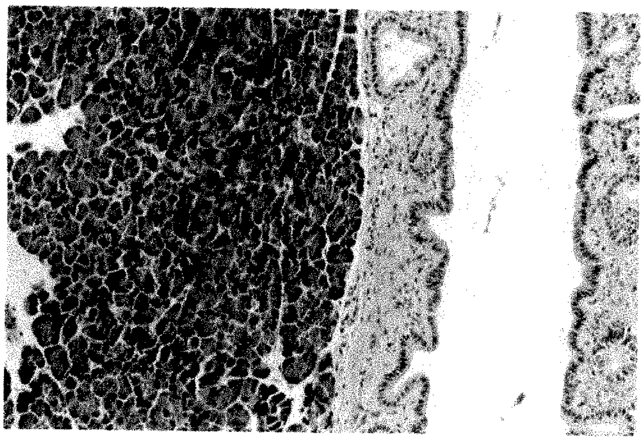


Fig 1.—Photomicrograph of pancreas from a control rat (group 1) (hematoxylin-eosin, original magnification × 100).

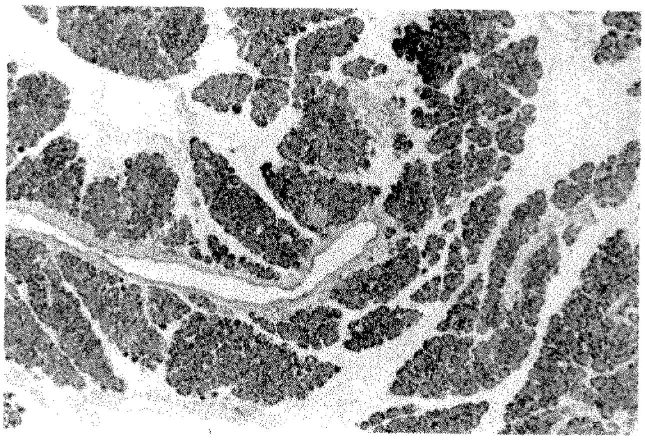


Fig 2.—Photomicrograph of pancreas from cerulein-treated rat. Prominent interstitial edema with separation of pancreatic lobules is evident (hematoxylin-eosin, original magnification × 40).

Fig 3.—Photomicrograph of pancreas from cerulein-treated rat. Numerous vacuoles are present within acinar cells (hematoxylin-eosin, original magnification × 100).

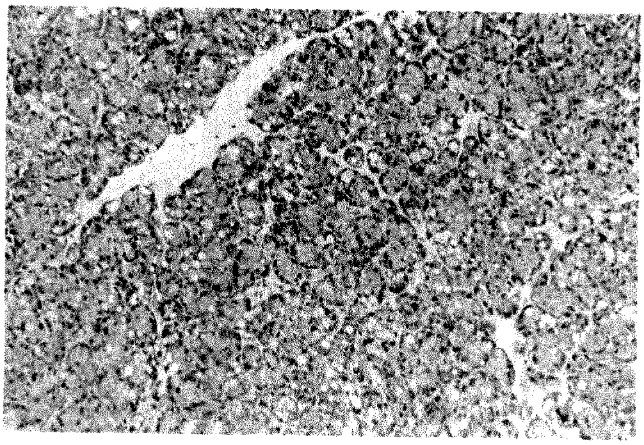
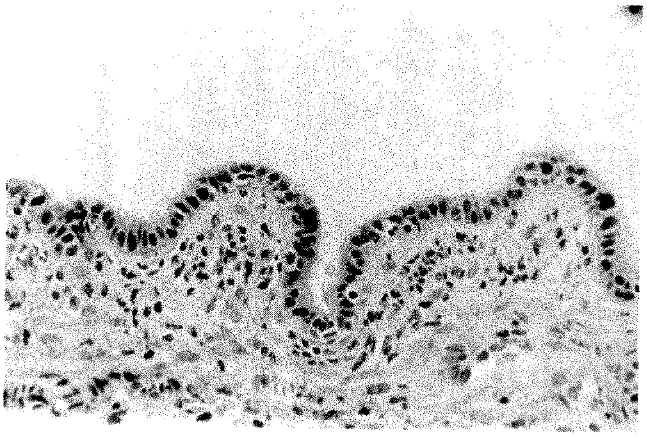


Fig 4.—Photomicrograph of pancreatic duct from cerulein-treated rat. Prominent periductal granulocyte infiltration in submucosa is present (hematoxylin-eosin, original magnification × 250).



ty of this form of experimental acute pancreatitis.

Because supramaximal cerulein administration induces acute pancreatitis by specific stimulation of cholecystokinin receptors and is prevented by a cholecystokinin antagonist,[15] we thought that inhibition of pancreatic secretion by octreotide may also prevent or ameliorate the pancreatic inflammation induced by supramaximal cerulein. We administered a dose of octreotide that is known to inhibit pancreatic and intestinal secretions.[16] We did not administer larger doses of octreotide because higher-dose octreotide decreases pancreatic blood flow,[17] an effect that is potentially detrimental in rats with coexisting acute pancreatitis.

Octreotide administration alone had no significant effect on basal plasma amylase concentration and wet pancreas weight. Octreotide reduced plasma amylase concentration by 39% and wet pancreas weight by 29% in rats with cerulein-induced acute pancreatitis, but these apparent improvements did not reach statistical significance by analysis of variance. These measures of pancreatitis severity (plasma amylase concentration, wet pancreas weight) in octreotide–treated rats with cerulein-induced acute pancreatitis were greater than basal values from control rats without acute pancreatitis (groups 1 and 2), but the difference was statistically significant only for amylase concentration. In addition, octreotide had no beneficial effect on the morphologic changes induced by supramaximal cerulein administration.

There are variable results from octreotide treatment of different experimental acute pancreatitis preparations. Lankisch et al[18] observed a reduction of serum amylase and lipase concentrations but did not find any beneficial effect of octreotide on pancreatic structure and survival in rats with acute pancreatitis caused by retrograde injection of bile into the pancreatic duct. Schwedes et al[4] reported less pancreatic damage in octreotide-treated dogs with acute pancreatitis caused by retrograde injection of bile into the pancreatic duct. Adler et al[5] demonstrated that octreotide inhibited newly synthesized enzyme and protein discharge from rat pancreatic lobules evoked by low-dose cerulein; octreotide reduced the severity of and improved recovery from acute pancreatitis induced by high-dose cerulein.

Baxter et al[6] demonstrated that octreotide prevented both the increase in serum concentration of pancreatic enzymes and the development of pancreatic inflammatory changes in acute pancreatitis caused by pancreatic duct and bile duct obstruction in rats. If these beneficial effects reported by Baxter et al[6] occur because octreotide inhibits discharge of acinar cell enzymes and protein, then the different results that we obtained with cerulein-induced acute pancreatitis are possibly explained by an inability of a clinically practical dose of octreotide to inhibit the profound pancreatic stimulation induced by supramaximal cerulein administration.

We conclude from these observations that octreotide had little overall benefit in treating cerulein-induced acute pancreatitis. To know whether octreotide, other pancreatic exocrine inhibitors,[19-21] or other new agents will be effective in the treatment of patients with acute pancreatitis, requires the development of more unifying concepts and a better understanding of acute pancreatitis pathogenesis.

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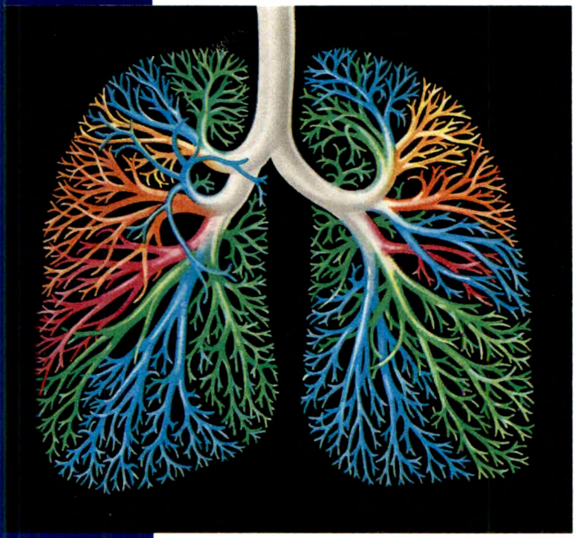
THE RESPIRATORY SEASON MEANS



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* Achieves 96% favorable clinical response (resolution + improvement) of infections due to susceptible strains of indicated pathogens. See indicated organisms in prescribing information.

† In vitro activity does not necessarily imply a correlation with in vivo results.

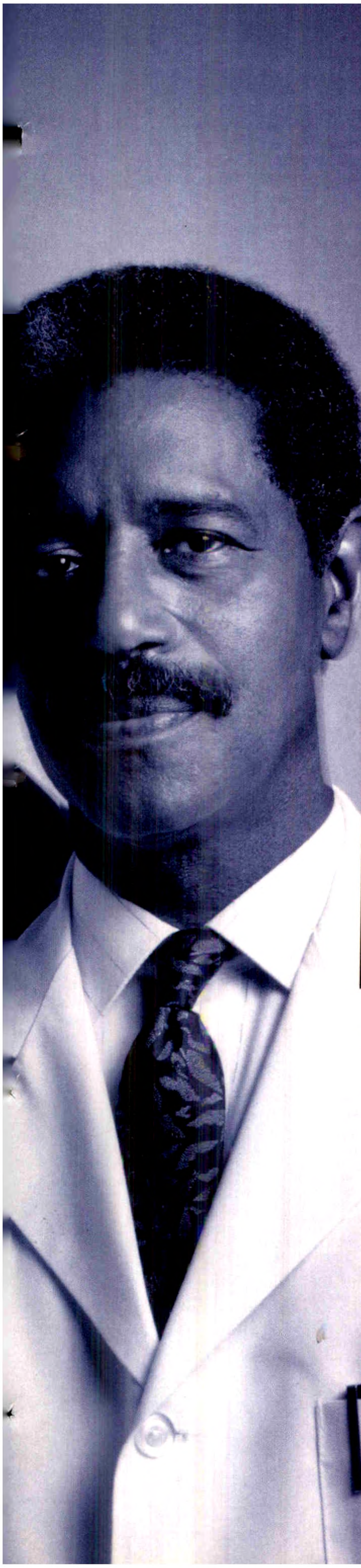
NOTE: Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Antacids containing magnesium hydroxide or aluminum hydroxide interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

CIPRO® SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN.

See last page for brief summary of prescribing information.



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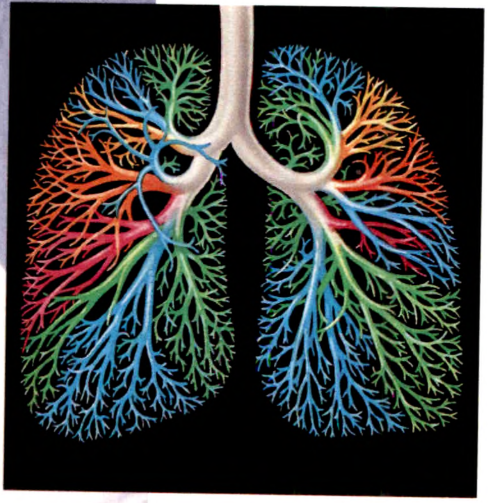
CIPRO® MAKES A TOUGH THERAPEUTIC CHOICE EASIER.



Treating patients with lower respiratory infections is often a challenge.

These patients may smoke or drink excessively, or have underlying conditions such as COPD.

They could be elderly or immunocompromised or live in nursing homes where they are constantly exposed to multiple organisms.

Too often, they may have a history of repeated antibiotic use that has proven ineffective against their lower respiratory infections.

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BRIEF SUMMARY
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INDICATIONS AND USAGE

Cipro® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Lower Respiratory Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*.

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*,* and *Shigella sonnei** when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Anaphylactic reactions following the first dose have been reported in patients receiving therapy with quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reaction. Anaphylactic reactions may require epinephrine and other emergency measures. Ciprofloxacin should be discontinued at the first sign of hypersensitivity or allergy.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have been reported rarely (less than one per million prescriptions) in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any sign of other hypersensitivity reaction.

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION). Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded.

Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION).

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Drug Interactions: As with other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with a quinolone has been reported to increase the risk of CNS stimulation and convulsive seizures.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum.

Patients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight in vitro mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- *E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V_{79} Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Patients under the age of 18 were not included in the clinical trials of ciprofloxacin because ciprofloxacin as well as other quinolones causes arthropathy in immature animals. Ciprofloxacin should not be used in children or adolescents (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%). Those events typical of quinolones are italicized.

The most frequently reported events, drug related or not, were *nausea* (5.2%), *diarrhea* (2.3%), *vomiting* (2.0%), *abdominal pain/discomfort* (1.7%), *headache* (1.2%), *restlessness* (1.1%), and *rash* (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below.

GASTROINTESTINAL: *(See above)*, painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: *(See above)*, *dizziness*, *lightheadedness*, *insomnia*, *nightmares*, *hallucinations*, *manic reaction*, *irritability*, *tremor*, *ataxia*, *convulsive seizures*, *lethargy*, *drowsiness*, *weakness*, *malaise*, *anorexia*, *phobia*, *depersonalization*, *depression*, *paresthesia*.

SKIN/HYPERSENSITIVITY: *(See above)*, *pruritus*, *urticaria*, *photosensitivity*, *flushing*, *fever*, *chills*, *angioedema*, *edema of the face*, *neck*, *lips*, *conjunctivae or hands*, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported (SEE PRECAUTIONS).

SPECIAL SENSES: *blurred vision*, *disturbed vision (change in color perception, overbrightness of lights)*, *decreased visual acuity*, *diplopia*, *eye pain*, *tinnitus*, *hearing loss*, *bad taste*.

MUSCULOSKELETAL: *joint or back pain*, *joint stiffness*, achiness, neck or chest pain, flare-up of gout.

RENAL/UROGENITAL: *interstitial nephritis*, *nephritis*, *renal failure*, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Other adverse events reported in the postmarketing phase include anaphylactoid reactions, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hepatic necrosis, postural hypotension, possible exacerbation of myasthenia gravis, confusion, dysphasia, nystagmus, pseudomembranous colitis, dyspepsia, flatulence, and constipation. Also reported were agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria, vaginal candidiasis; and renal calculi (SEE PRECAUTIONS).

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic—Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Cholestatic jaundice has been reported.

Hematologic—Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.[illegible]%), pancytopenia (0.1%).

Renal—Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Lower respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro® (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE DESCRIPTION).

References: **1** Data on file, Miles Inc Pharmaceutical Division. **2.** Barry AL, Jones RN, Thornsberry C, et al. Antibacterial activities of ciprofloxacin, norfloxacin, oxolinic acid, cinoxacin, and nalidixic acid. *Antimicrob Agents Chemother.* 198[illegible];25:633-637. **3.** Guimaraes MA, Noone P. The comparative *in-vitro* activity of norfloxacin, ciprofloxacin, enoxacin and nalidixic acid against 423 strains of gram-negative rods and staphylococci isolated from infected hospitalized patients. *J Antimicrob Chemother.* 1986;17:63-67. **4.** Van Caekenberghe DL, Pattyn SR. In vitro activity of ciprofloxacin compared with those of other new fluorinated piperazinyl-substituted quinolone derivatives. *Antimicrob Agents Chemother.* 1984;25:518-521.

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Absorptive Hyperemia Restores Intestinal Blood Flow During *Escherichia coli* Sepsis in the Rat

John R. Gosche, MD; R. Neal Garrison, MD; Patrick D. Harris, PhD; H. Gill Cryer, MD, PhD

• Enteral nutritional support has been found to result in better maintenance of mucosal integrity during stress than parenterally administered nutritional support. In our experiments, we employed in vivo microvascular techniques to examine the effect of mucosally applied glucose on intestinal microvascular blood flow during hyperdynamic live *Escherichia coli* bacteremia in the rat. We observed a significant decrease in intestinal microvascular blood flow during bacteremia when the mucosa was suffused with a nonglucose solution. Blood flow was rapidly restored to above-baseline values after glucose was added. The restoration of blood flow resulted from dilation of arterioles at all branch orders and was associated with dilation of premucosal arterioles to above-baseline diameters. Our results show that glucose-induced absorptive hyperemia restores intestinal blood flow during live *E coli* bacteremia. Restoration of intestinal microvascular blood flow may be a contributing factor to the improved maintenance of mucosal integrity associated with enteral feeding.

(*Arch Surg*. 1990;125:1573-1576)

The neural, hormonal, and inflammatory responses that accompany severe stress decrease intestinal blood flow, leading to mucosal ischemic damage, loss of mucosal barrier function, and translocation of bacteria and bacterial products.[1-3] This sequence of events could account for the high incidence of persistent sepsis and multisystem organ failure that follows many traumatic injuries.[4,5] Enterally administered nutritional support prevents mucosal weight loss, increases epithelial proliferation, and improves the maintenance of gut mucosal integrity.[6,7] These benefits are not generally achieved with parenteral nutrition.[8-10] Several investigators have suggested that this trophic benefit of intraluminally supplied nutrients on the gut mucosa is derived from the improved supply of absorbed nutrients to the mucosal epithelium or from the release of trophic hormones.[6-9] In contrast, this trophic benefit could reflect an improved mucosal blood flow from hyperemia induced by the transmucosal absorption of intraluminal nutrients.[11]

We tested the feasibility of the latter possibility by determining if a mucosally applied nutrient (glucose) could induce a hyperemia that would overcome the perfusion deficit in the intestinal microcirculation that occurs during bacteremia. Our results indicate that mucosal exposure to glucose restores intestinal microvascular blood flow to above-baseline levels during sepsis.

MATERIALS AND METHODS

Male Sprague-Dawley rats, weighing between 160 and 200 g, were acclimated in an American Association for Accreditation of Laboratory Animal Care–approved animal care facility and were maintained on standard rat food (15 g/d, Purina Mills Inc, Louisville, Ky) and water as desired for at least 2 weeks. Food, but not water, was withdrawn at least 12 hours before each microcirculation experiment. Animals were anesthetized initially with intraperitoneal urethane (800 mg/kg) and chloralose (60 mg/kg) and were administered one fourth of the initial anesthetic dose at approximately 1-hour intervals. During the surgical preparation and subsequent experiments, rectal temperature was maintained at 37°C ± 0.5°C using a back heater and radiant heat source.

A tracheostomy tube was placed for airway control, and the animals were allowed to breathe spontaneously. The right jugular vein was cannulated, and a tissue thermistor (Model 511, Yellow Springs [Ohio] Instrument Co) was introduced via the right carotid artery for measurement of cardiac output by transpulmonary thermodilution. The left femoral artery was cannulated for monitoring blood pressure. We modified the previously described[1] preparation of the small intestine for in vivo videomicroscopy. A 2- to 3-cm segment of ileum was exposed through a vertical abdominal incision and was opened along its antimesenteric border by electrocautery. The opened intestinal loop, with intact neurovascular connections, was suspended over the optical window in a tissue bath that we modified to allow separate suffusion of the serosal and mucosal surfaces (Fig 1). The exposed intestinal segment was maintained at 36°C ± 2°C using a radiant heat source and feedback control system.

The suffusate was a modified Krebs solution that contained 6.92 g/L of sodium chloride, 0.44 g/L of potassium chloride, 0.37 g/L of calcium chloride, and 2.1 g/L of sodium bicarbonate. The suffusion solution was heated to maintain temperature at 37°C ± 1°C and bubbled with a mixture of carbon dioxide and nitrogen to maintain pH at 7.40 ± 0.05. A low concentration of isoproterenol hydrochloride (1×10^{-8} g/mL) was added to all suffusion solutions to quiet peristalsis and assist recording of microvessel diameters and centerline red blood cell velocities. The addition of isoproterenol in concentrations as much as 1000 times that used in this study are reported to have no effect on microvessel diameters or vasoreactivity.[12] During some protocols, 1 mL of a 5% concentration of dextrose in water was added to 99 mL of the Krebs solution to give a final dextrose concentration of 1 g/L in the suffusate to the mucosal surface. This glucose Krebs solution was isotonic, which avoided the hyperemic effects of hypertonic solutions.[11]

Fourteen animals were divided into three groups. After the surgical preparation, the animals were transferred to the microscope stage and allowed at least 30 minutes for blood pressure and tissue conditions to stabilize. Two baseline measurements of cardiac output, mean arterial pressure, heart rate, microvessel diameters, and red blood cell velocity in the A1 arteriole were recorded. Group 1 (n = 5) received 1 mL of intravenous saline (vehicle) and was observed at 10-minute intervals for 60 minutes (period 1), while the serosal and mucosal surfaces of the exposed intestinal segment were suffused with a nonglucose Krebs solution. Glucose was then added to the Krebs solution, suffusing the mucosal surface, while observations continued for an additional 60 minutes (period 2). Group 2 (n = 4) received 1 mL of the bacterial suspension intravenously and was observed at 10-minute intervals for 120 minutes (periods 1 and 2),

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Read before the 14th Annual Surgical Symposium of the Association of Veterans Affairs Surgeons, Charleston, SC, May 7, 1990.

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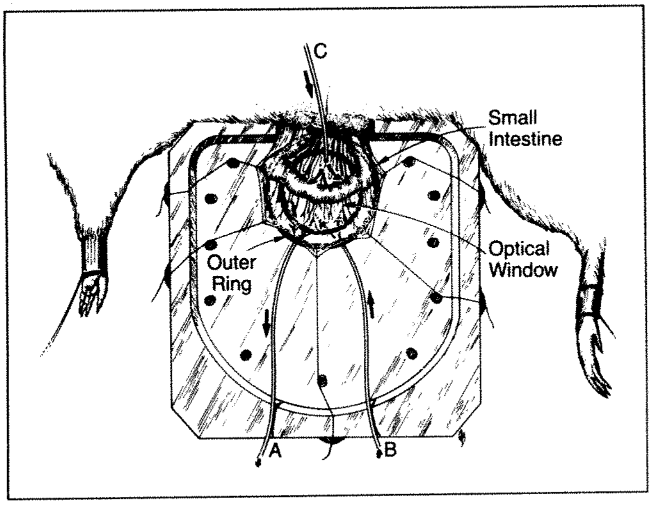

Fig 1.—The tissue board was modified by placing a plastic ring outside the optical window, allowing separate suffusion of the mucosal and serosal surfaces. A indicates suction port; B, mucosal suffusate; and C, serosal suffusate.

while the serosal and mucosal surfaces were suffused with the nonglucose Krebs solution. Group 3 (n = 5) was treated the same as group 2 during period 1. Glucose was then added to the Krebs solution suffusing the mucosal surface, and observations were continued during period 2.

A hospital-acquired pathogenic strain of *Escherichia coli* bacteria was grown in tryptose-soy broth to obtain a stationary growth-phase culture. The bacteria were then centrifuged and washed twice with sterile saline. Serial dilutions were performed in saline to give a final bacterial concentration of 1×10^{12}/L *E coli* as determined by spectrophotometric density at 550 nm. Bacterial concentrations of the final dilution were confirmed by quantitative cultures.

Transpulmonary thermodilution cardiac output was determined as described by Cooper et al.[13] Room temperature saline (40 μL) was injected via the right jugular venous catheter, and time-temperature curves were generated via a thermistor positioned in the aortic root. Cardiac output was calculated from the area under the time-temperature curve. Three separate determinations were averaged to give cardiac output at each time point.

Centerline red blood cell velocity was measured in the first-order arteriole via an in-line optical Doppler velocimeter (Microvascular Research Institute, Texas A&M University, College Station). This dual slit technique allows accurate, serial measurements of red blood cell velocities at different microvascular levels without altering or disrupting flow within the microcirculation. Blood flow through the first-order arteriole was calculated by the following formula:

$$(K)(\text{average cross-sectional velocity})(\pi)(\text{A1 radius})^2$$

Average cross-sectional velocity was calculated as the centerline velocity divided by 1.6.[14] The constant K represents 6×10^{-5} and was used to convert flow into microliters per minute.

The intestinal microvasculature was observed via a trinocular microscope, and television images were recorded on videotape for later measurement of intraluminal diameters. First- through fourth-order arterioles, distal third-order premucosal arterioles, and first- and second-order venules[15] were recorded at 10-minute intervals. Intraluminal vessel diameters were measured in triplicate from a videotape replay on a television monitor. Microvessel diameters were obtained by multiplying the monitor measurements by a magnification factor (6.65×10^{-4}) that had previously been determined through calibration of the microscope-television system by a microscope-stage micrometer.

Blood flow and baseline microvessel diameters were variable among animals depending on the amount of tissue being perfused. To minimize the effect of this variability on subsequent data analysis, changes in vessel diameter and blood flow were normalized to baseline values and were expressed as a percentage of baseline values in each animal. Significant changes from baseline values within groups were determined by Dunnett's test after repeated-measures analysis of variance (ANOVA) (non-normalized values). Group differences were determined on the normalized data by Tukey's Honestly Significant Difference after one-way ANOVA for unpaired observations. Differences were considered significant at $P = .05$. All values are expressed as group means ± SEMs.

Comparison of Baseline Values

Variable*	Group 1 (n=5)	Group 2 (n=4)	Group 3 (n=5)
MAP, mm Hg	99±7	103±5	100±5
CO, mL/min	81±6	79±8	78±9
A1 Flow, μL/min	11±1	12±2	11±2
A1 Diameter, μm	89±9	85±4	85±5
Proximal A3, μm	25±2	21±1	21±2
Distal A3, μm	16±.09†	13±0.4	13±0.4
A4 Diameter, μm	12±1	12±1	13±1
V1 Diameter, μm	201±21	189±11	215±16
V2 Diameter, μm	145±18	134±4	170±21

*MAP indicates mean arterial pressure, and CO, cardiac output.

†$P<.05$ from groups 2 and 3 by analysis of variance and Tukey's Honestly Significant Difference.

RESULTS

Experimental conditions (ie, rectal temperature, tissue temperature, suffusate temperature, and pH) were comparable among the three groups. Baseline values for mean arterial pressure, cardiac output, intestinal first-order blood flow, and microvessel diameters were comparable among the three groups, with one exception (Table). The baseline diameters for the distal third-order arterioles were slightly greater in group 1 (nonseptic) than in group 2 (nonglucose septic) and group 3 (glucose-treated septic). Mean arterial pressure was significantly greater in group 2 than in the other two groups at the end of period 1 and at the beginning of period 2 (Fig 2). Cardiac output differences were not statistically significant between groups. Group analysis revealed significant ($P<.05$) increases in cardiac output in groups 2 and 3 at the end of period 1, while no statistically significant changes were observed in group 1.

Intestinal blood flow (Fig 3) did not change significantly during period 1 in group 1. Blood flow significantly decreased at the end of period 1 in groups 2 and 3 and continued to decline during period 2 in group 2. Blood flow in group 3 increased to baseline levels within 20 minutes after the mucosa was exposed to glucose. There were no significant differences in first-order blood flow between groups 1 and 3 at the end of period 2, but both of these glucose groups had significantly greater first-order intestinal flows than the group 2 animals. Arteriolar diameter differences (Fig 4) were statistically significant between groups 1 and 2 for the first-order arterioles at the end of period 1. Statistically significant differences between group 2 and the other two groups were observed at all arteriolar levels at the end of period 2. In contrast, there were no differences between groups 1 and 3 during period 2.

COMMENT

Controversy continues regarding the relative benefits of enteral vs parenteral alimentation. In addition to economic considerations and ease of application, nutritional support by the enteral route appears to have other important physiologic benefits. Enteral alimentation maintains epithelial cell proliferation and mucosal integrity better than parenteral nutritional support.[6,7] This benefit might be of particular importance because of the increasing evidence that the gut could be an important source of persistent sepsis[3,4] resulting from the

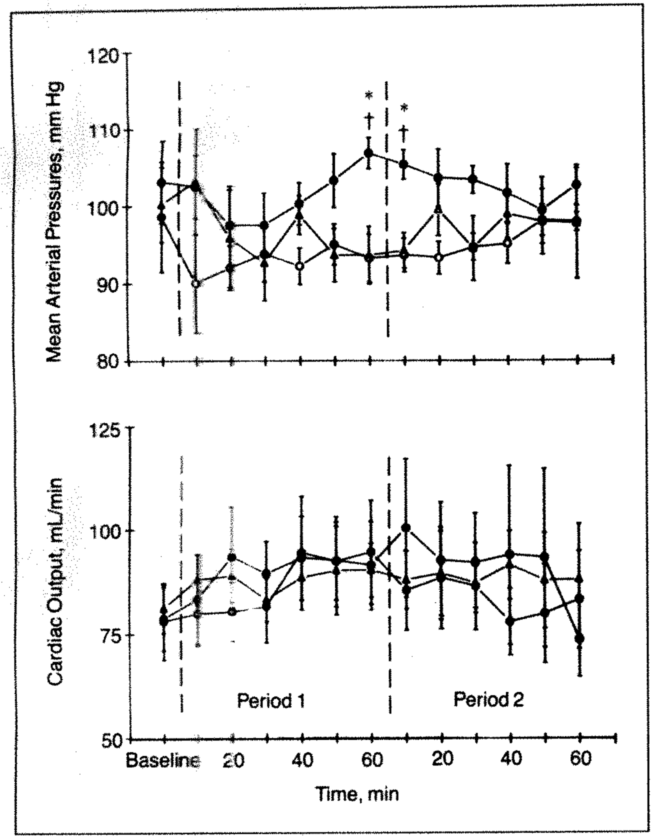

Fig 2.—Changes in mean arterial pressure and cardiac output over time for the three treatment groups. Triangles represent group 1 (saline/glucose); solid circles, group 2 (*Escherichia coli*/no glucose); open circles, group 3 (*E coli*/glucose); asterisk, $P<.05$ for group 1 vs group 2; and dagger, $P<.05$ for group 2 vs group 3 by analysis of variance with Tukey Honestly Significant Difference.

loss of mucosal barrier function due to mucosal ischemia during severe stress.

The mechanism by which enterally supplied nutrition maintains mucosal integrity remains unknown. Improved delivery of energy to the epithelial cells of the gut has been proposed,[6-9] but intraluminal nutrients also cause release of gastrointestinal peptide hormones (ie, glucagon and gastrin) that have trophic effects on the intestinal mucosa.[6,8,16] Our data suggest that improved maintenance of mucosal integrity during shock could result from a direct hyperemic response to intraluminal nutrients that restores intestinal microvascular blood flow to normal levels.

Clearly, factors other than the direct hyperemic effect of intraluminal nutrients influence intestinal blood flow during feeding under normal conditions.[17] However, under the conditions of our experiments, systemic influences (ie, release of gastrointestinal hormones) probably had little effect, since the concentration of glucose and the area of intestine exposed to glucose were small. Thus, the hyperemic effects that we observed were most likely a result of local vasoactive mechanisms that occurred at the microvascular level. From this viewpoint, one might expect an even greater increase in overall intestinal blood flow when gut hormonal responses are activated in addition to these local vasoactive mechanisms.

The hyperemic effect of glucose absorption was associated with a generalized dilation of arterioles at all levels in our study. These results are similar to those of Bohlen,[11] who reported a generalized vasodilator response to glucose. Chou et al,[18] however, noted only a localized increase in blood flow to the mucosa when a predigested meal was placed in the gut lumen. The reason for the differences in blood flow responses among these studies probably relates to differences in experimental design. The conditions of our study were similar to those of the study by Bohlen, but the study by Chou et al used a different species and a different means to induce hyperemia (ie, bolus of a predigested meal). Thus, it is likely that the selective hyperemia observed by Chou et al was the result of the combined effect of a direct absorptive hyperemia and of the release of gut vasoactive hormones and intestinal neural reflexes. Siregar and Chou[19] have shown that meals containing a high fat content cause greater increases in intestinal blood flow than high-carbohydrate meals, while complex solutions containing protein, carbohydrate, and fat induce larger hyperemic responses than solutions containing equivalent amounts of any individual constituent. Collectively, these studies suggest the possibility that feeding of a more complex foodstuff might result in a larger increase in blood flow and more selective redistribution of blood flow toward the mucosa during sepsis than was observed in our study. This hypothesis, however, remains to be tested.

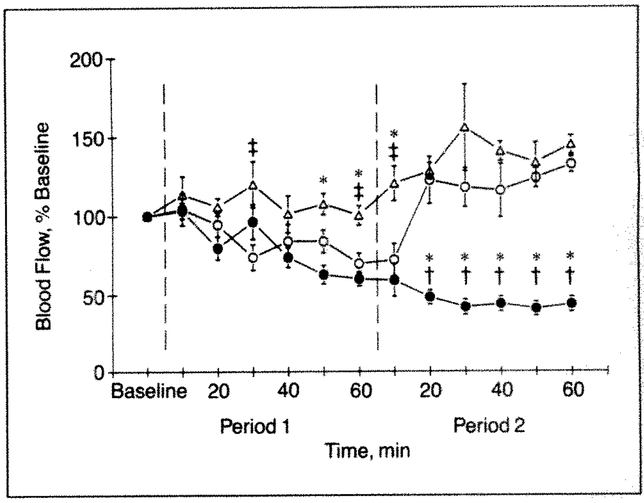

Fig 3.—Changes in blood flow through the first-order (A1) arteriole over time (expressed as percentage of baseline flow) for the three treatment groups. Triangles represent group 1 (saline/glucose); solid circles, group 2 (*Escherichia coli*/no glucose); open circles, group 3 (*E coli*/glucose; asterisk, $P<.05$ for group 1 vs group 2; dagger, $P<.05$ for group 2 vs group 3; and double dagger, $P<.05$ for group 1 vs group 3 by analysis of variance with Tukey Honestly Significant Difference.

Clearly, one must question whether the restoration of intestinal blood flow in our study was adequate to prevent mucosal ischemia, since nutrient absorption increases mucosal energy expenditure and oxygen requirements. Our results show that intestinal microvasculature blood flow increased in the septic animals to above-baseline levels. Furthermore, intestinal blood flow was increased to levels that were similar to those observed in nonseptic animals. These data, along with the fact that intestinal oxygen extraction is low under normal conditions, lead us to believe that the restoration of blood flow that we observed probably reduced the level of mucosal hypoxia during sepsis. However, since oxygen delivery might be altered and intestinal oxygen requirements might be increased during sepsis,[20,21] more experiments are required to confirm or refute our speculation.

In conclusion, our results show that the hyperemia induced by direct application of glucose to the mucosal surface of the small intestine is able to overcome the flow-restrictive effect of live *E coli* bacteremia. Restoration of blood flow appears to have been the result of a reversal in arteriolar vasoconstriction that occurs at multiple levels in the intestinal microcirculation during hyperdynamic sepsis. We suggest that this

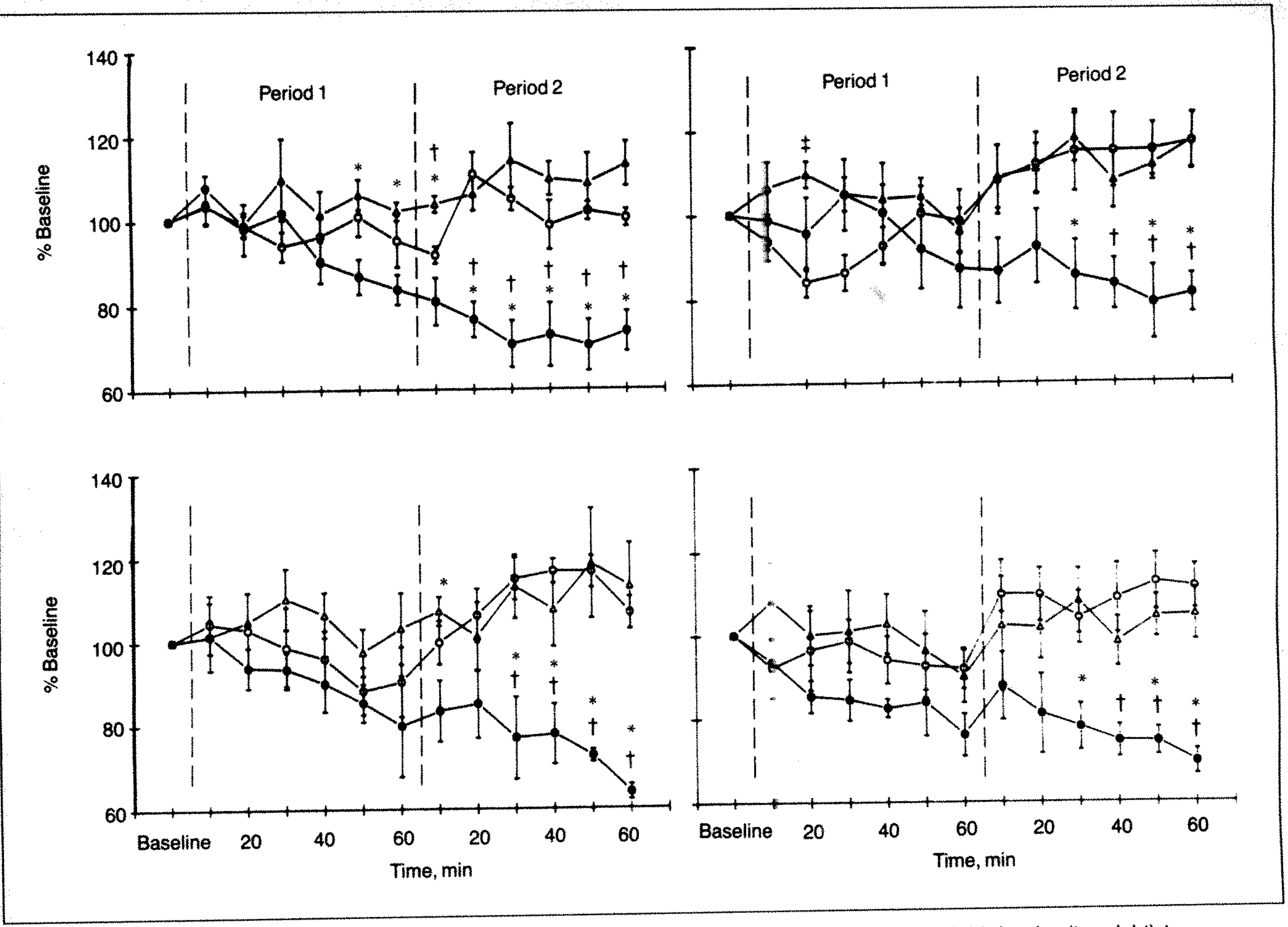

Fig 4.—Changes in diameters of first-order (top left), proximal third-order (bottom left), distal third-order (top right) to mucosal tissue and fourth-order (bottom right) to the serosal tissue arterioles (expressed as percentage of baseline diameters) over time for the three treatment groups. Triangles represent group 1 (saline/glucose); solid circles, group 2 (*Escherichia coli*/no glucose); open circles, group 3 (*E coli*/glucose); asterisk, $P<.05$ for group 1 vs group 2; dagger, $P<.05$ for group 2 vs group 3; and double dagger, $P<.05$ for group 1 vs group 3 by analysis of variance with Tukey Honestly Significant Difference.

direct hyperemic effect of transmucosal absorption of nutrients on the intestinal microvasculature is one factor that accounts for the improved maintenance of mucosal integrity associated with enteral alimentation.

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We acknowledge the technical assistance of Jean Jenkins and Rebecca Galloway. John M. Yancey, PhD, University of Louisville, assisted with statistical analysis.

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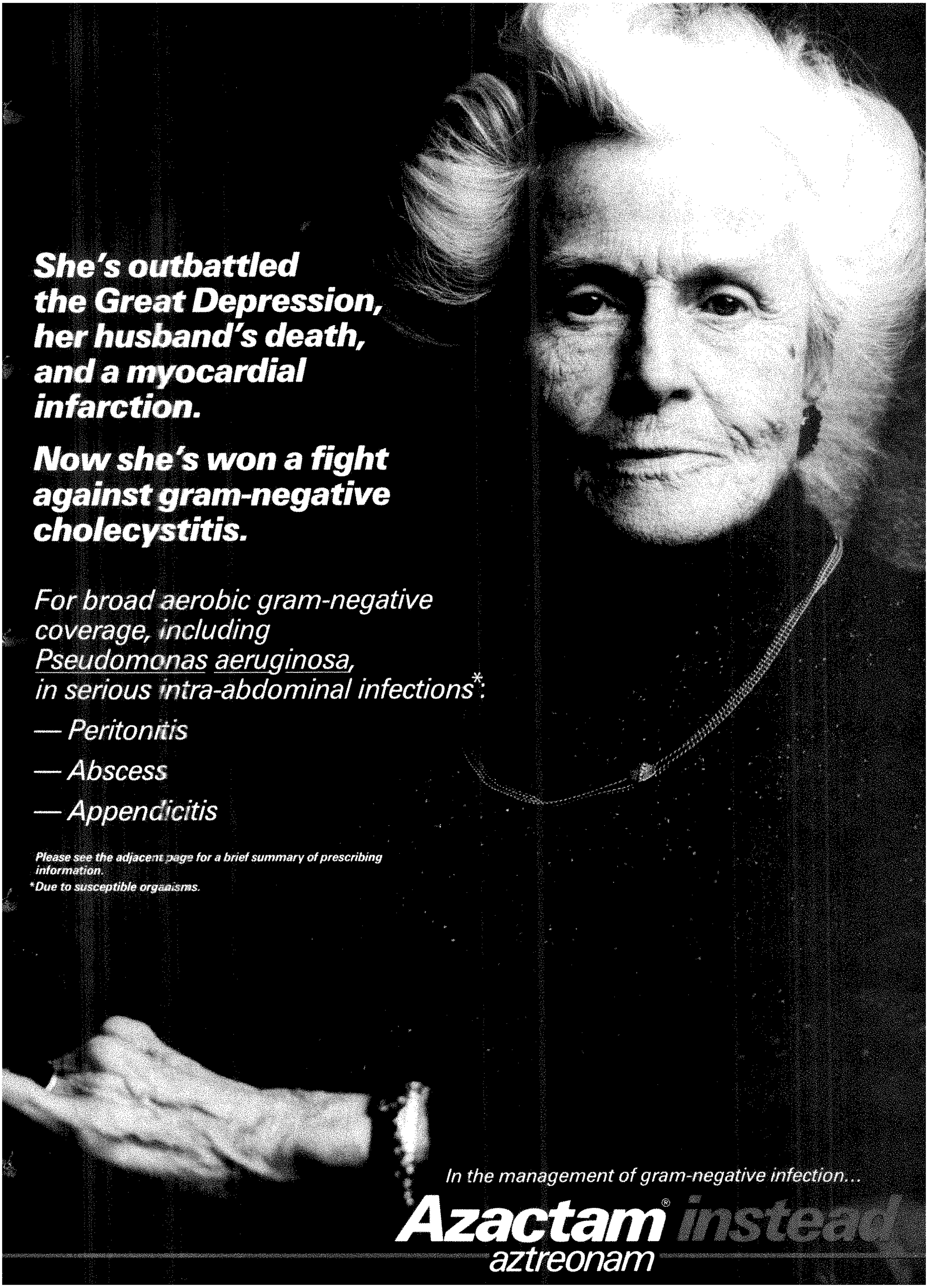

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DESCRIPTION—AZACTAM (aztreonam, Squibb) is the first member of a new class of antibiotics classified as monobactams. AZACTAM is a totally synthetic bactericidal antibiotic with activity against a wide spectrum of gram-negative aerobic pathogens. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics.

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INDICATIONS AND USAGE—Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of the susceptibility testing are available; subsequently, appropriate antibiotic therapy should be continued.

AZACTAM For Injection is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: **Urinary Tract Infections** (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella oxytoca**, *Citrobacter* species* and *Serratia marcescens**. **Lower Respiratory Tract Infections,** including pneumonia and bronchitis caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae, Proteus mirabilis, Enterobacter* species and *Serratia marcescens**. **Septicemia** caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis**, *Serratia marcescens** and *Enterobacter* species. **Skin and Skin-Structure Infections,** including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli, Proteus mirabilis, Serratia marcescens, Enterobacter* species, *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Citrobacter* species*. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli, Klebsiella* species, including *K. pneumoniae, Enterobacter* species including *E. cloacae**, *Pseudomonas aeruginosa, Citrobacter* species* including *C. freundii** and *Serratia* species* including *S. marcescens**. **Gynecologic Infections,** including endometritis and pelvic cellulitis caused by *Escherichia coli, Klebsiella pneumoniae**, *Enterobacter* species* including *E. cloacae**, and *Proteus mirabilis**.

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

Concurrent Therapy—Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected, therapy should be initiated using an antianaerobic agent concurrently with AZACTAM. Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing, appropriate antibiotic therapy should be continued.

CONTRAINDICATION—Aztreonam is contraindicated in patients with known allergy to this antibiotic.

WARNINGS—Careful inquiry should be made for a history of hypersensitivity reaction to any antibiotic or other drugs. Antibiotics should be given with caution to any patient who has had some form of allergy, particularly to drugs. It is recommended that patients who have had immediate hypersensitivity reactions (e.g., anaphylactic or urticarial) to penicillins and/or cephalosporins should be followed with special care. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures.

PRECAUTIONS—General: In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy. If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenicity studies in animals have not been performed. Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level. Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

Pregnancy—Pregnancy Category B: Aztreonam crosses the placenta and enters the fetal circulation. Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Nursing Mothers—Aztreonam is excreted in breast milk in concentrations that are less than 1% of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

Pediatric Use—Safety and effectiveness have not been established in infants and children.

ADVERSE REACTIONS—Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9% and 2.4%, respectively. Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3% include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity: *Hypersensitivity*—anaphylaxis. *Hematologic*—pancytopenia, neutropenia, thrombocytopenia, anemia, leukocytosis, thrombocytosis. *Gastrointestinal*— abdominal cramps; rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. *Dermatologic*—purpura, erythema multiforme, urticaria, exfoliative dermatitis, petechiae, pruritus, diaphoresis. *Cardiovascular*—hypotension, transient ECG changes (ventricular bigeminy and PVC). *Respiratory*—one patient experienced flushing, chest pain, and dyspnea. *Hepatobiliary*—hepatitis, jaundice. *Nervous System*—seizure, confusion, vertigo, paresthesia, insomnia, dizziness. *Musculoskeletal*—muscular aches. *Special Senses*—tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing and nasal congestion, halitosis. *Other*—vaginal candidiasis, vaginitis, breast tenderness. *Body as a Whole*—weakness, headache, fever, malaise.

Adverse Laboratory Changes—Those reported without regard to drug relationship during clinical trials were: *Hepatic*—elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1% of recipients (see above). *Hemic*—increases in prothrombin and partial thromboplastin times, eosinophilia, positive Coombs test. *Renal*—increases in serum creatinine.

OVERDOSAGE—If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

DOSAGE AND ADMINISTRATION—Dosage adjustments are recommended for patients with impaired renal function. In elderly patients, estimates of creatinine clearance should be obtained and appropriate dosage modifications made if necessary.

HOW SUPPLIED—AZACTAM For Injection (Aztreonam For Injection)—Lyophilized—is supplied in single-dose 15 mL vials containing **500 mg,** or **1 g**/vial; in single-dose 30 mL vials containing **2 g**/vial; and in single-dose 100 mL intravenous infusion bottles containing **500 mg** or **1 g** or **2 g**/bottle.

Consult package insert before prescribing AZACTAM (aztreonam).

(J4-231A)

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*Efficacy for this organism in this organ system was studied in fewer than ten infections.

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Venous Hemodynamics in a Chronic Venous Valvular Insufficiency Model

Stephen G. Lalka, MD; Joseph L. Unthank, PhD; Michael C. Dalsing, MD; Dolores F. Cikrit, MD; Alan P. Sawchuk, MD

• To develop a large-animal model of chronic venous valve incompetence, 13 greyhound dogs underwent unilateral hindlimb venous valve lysis with a valve cutter apparatus pulled retrograde through the iliac, femoral, and lateral saphenous veins. Bilateral venous pressures in the lateral saphenous vein were recorded before valve lysis, immediately after valve lysis, and at intervals from 1 to 14 weeks after valve lysis, with the dogs in the supine position and elevated 80° semierect, as well as after stimulated hindlimb muscle contraction to empty the hindlimb veins. Passive venous filling time with elevation and 90% venous refilling time after muscle contraction were calculated. From immediately after through 14 weeks after valve lysis, a shortened venous filling time and 90% venous refilling time as well as an elevated poststimulation venous pressure were noted. This valve lysis method successfully produced a hemodynamically verified model of venous valvular insufficiency.

(*Arch Surg.* 1990;125:1579-1583)

Because of the debilitating nature of venous valvular insufficiency and its effect on a relatively young, otherwise healthy population, deep venous reconstructive surgery has recently been the focus of major research.[1] Transplantation of autogenous valve-bearing segments and the development of synthetic or biologic valve prostheses appear to be areas of particular investigative promise. However, one impediment to venous surgical research has been the absence of laboratory models that would allow controlled study of deep venous insufficiency and its surgical management.[2] Another problem has been the lack of objective physiologic data to support the application of various venous reconstructive techniques.[1]

The current study was designed to develop a stable, reproducible large-animal model of chronic venous valvular insufficiency. The efficacy of the model was hemodynamically assessed by serial venous pressure measurements.

MATERIALS AND METHODS

Thirteen adult greyhound dogs weighing 23 to 34 kg were sedated with intravenous xylazine hydrochloride (1 mg/kg), were anesthetized with intravenous pentobarbital sodium (30 mg/kg), and underwent ventilation with a volume-controlled ventilator via endotracheal intubation. All dogs received aspirin (325 mg orally) one day preoperatively and then daily during the postoperative period until they were killed. Cefazolin sodium (500 mg) was infused preoperatively and then injected intramuscularly for three additional doses during the first 30 hours postoperatively. Bilateral baseline venous pressure data (see below) were recorded on a chart recorder (Model 3200, Gould, Inc, Cleveland, Ohio) via pressure transducers connected to lateral saphenous vein catheters inserted just cephalad to the paw.

Valve Lysis

Once baseline data were obtained, the left saphenous vein catheter was removed and the left hindlimb was prepared and draped in a sterile fashion. At the percutaneous catheter entry site, a 1-cm transverse incision was made to expose the left lateral saphenous vein, which was encircled proximally with a No. 3-0 silk tie and ligated caudally. After the systemic administration of heparin sodium (150 U/kg), the previous percutaneous venotomy was enlarged with Potts scissors, and a modified retrograde valve cutter (Leather Valve Cutter, Baxter–V. Mueller, Chicago, Ill) was passed cephalad into the deep venous system to the level of the inferior vena cava. This valve lysis apparatus (Fig 1) consisted of a Silastic 3F thromboendarterectomy catheter with the balloon tip excised and 1 cm of the Silastic coating stripped off the underlying threaded wire. A drop of cyanoacrylate was placed on the wire before screwing on a 2-mm Leather valve cutter; this was held with firm pressure for 2 minutes to cement the cutter to the wire. The valve cutter is a detachable polystyrene device that is essentially two valvulotomes with their blades oriented at 180° to each other (Fig 1).

To distend the valve cusps and promote valve lysis, the operating table was tilted to place the dog in the 80° semierect position. A Valsalva maneuver was simulated by attaching a manual resuscitator to the endotracheal tube and compressing and holding the manual resuscitator in this position to prevent exhalation during the brief period of valve lysis. The valve cutter was then pulled caudad through the iliac, femoral, and lateral saphenous veins with a firm, continuous, rapid motion. Five to eight valves usually were encountered (Fig 2). The cutter occasionally met excessive resistance, indicating a branch point; this was managed by pushing the cutter cephalad, rotating it 45°, and then pulling it down through the remaining valve

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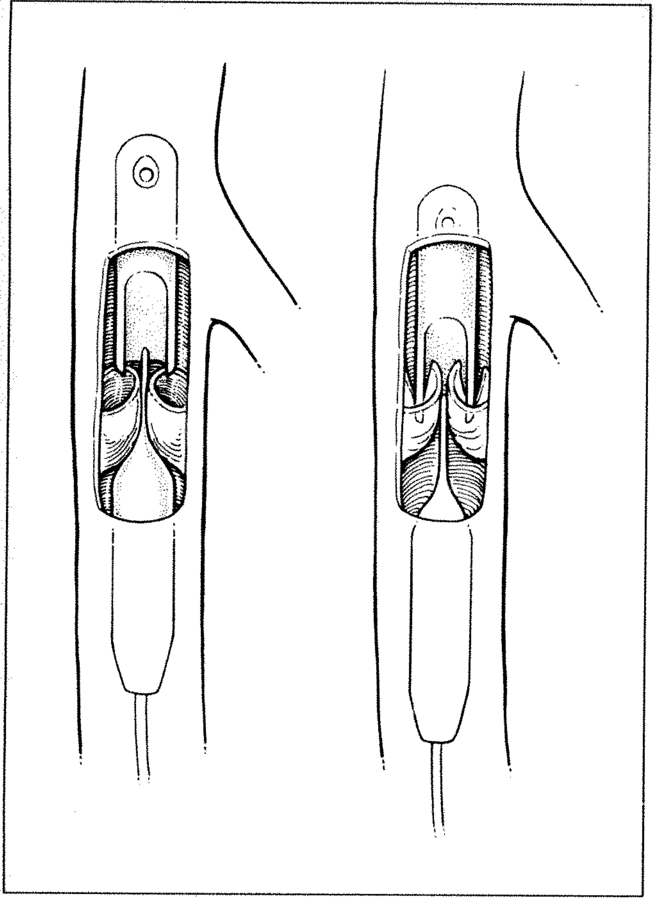

Fig 1.—Venous valve lysis with modified Leather valve cutter apparatus (Baxter–V. Mueller, Chicago, Ill).

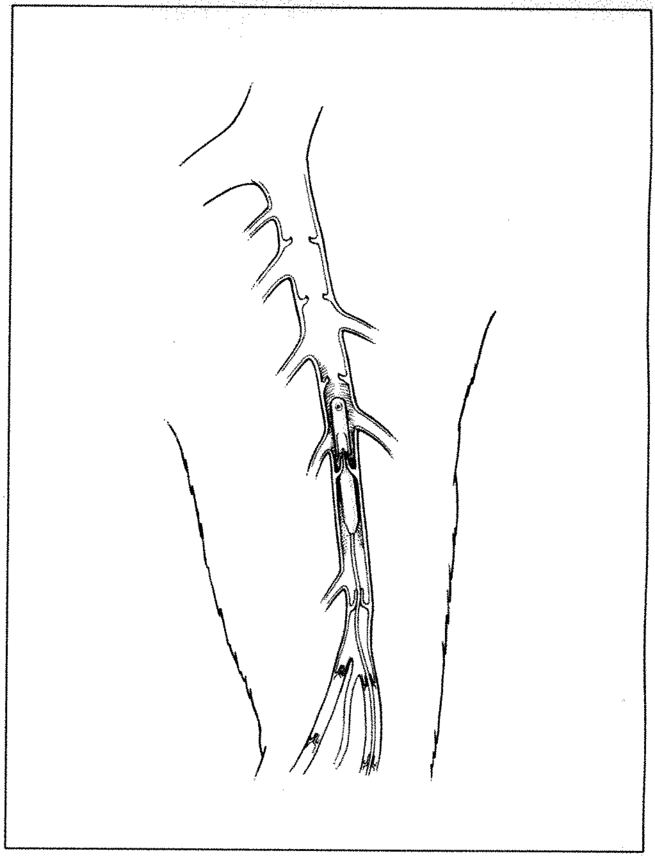

Fig 2.—Diagram of valve lysis procedure. Usually five to eight valves are encountered in the iliac, femoral, and lateral saphenous veins.

cusps. To achieve adequate ventilation, to lessen bleeding, and to ensure distention of any remaining competent valve cusps, the cutter was pulled through the vein in three sets of two passes each, with return of the table to the horizontal position for 1 to 2 minutes between each set of passes. If the venous pressure waveforms were inconsistent with valve incompetence (as defined below), additional sets of passes were made. Another cannula was then introduced through the lateral saphenous venotomy, through which lysis was performed, and connected to the pressure transducer to repeat the hemodynamic measurements; the right (control) hindlimb data were recorded via the same lateral saphenous vein catheter used for the baseline data. After data collection, the catheters were removed, the left saphenous vein was ligated cephalad to the venotomy, the incision was closed with interrupted monofilament sutures, and the dog was awakened.

Hemodynamic Data

Bilateral hindlimb venous pressures were recorded with the dog in the supine position (P_{SP}, Fig 3a) and then during rapid elevation to the 80° semierect position (P_{EL}, Fig 3b). This caused a rise in venous pressure until a plateau was reached, indicating a full hindlimb venous capacitance. The time that elapsed between the table tilt and the pressure plateau was recorded as the passive venous filling time (VFT). To empty the hindlimb venous system, vigorous hindlimb muscle contraction was induced with use of a peripheral nerve stimulator (Grass, Inc, Quincy, Mass) with 10 one-per-second applications of a 50-Hz, 100-V, 200-millisecond stimulus via electrodes inserted in the gracilis and biceps femoris muscles of the thigh. The 80° semierect resting pressure before stimulus (P_0) and the poststimulation mean asymptotic steady-state pressure (P.) were used to determine the 90% venous refilling time (VRT_{90}), defined as the time required for the venous pressure to return from its nadir at P. to 90% of the prestimulus semierect resting pressure calculated from the following formula: $0.9(P_0 - P.) + P.$ (Fig 3c).[3] These venous pressure measurements, with the dog in the supine position, in the upright position, and after hindlimb muscle contraction in the upright position, simulate clinical ambulatory venous pressure changes.[3]

These bilateral venous pressure data were recorded at baseline before lysis (T1), 5 minutes after valve lysis (T2), and at 1 to 2 weeks (T3), 3 to 5 weeks (T4), and 9 to 14 weeks (T5) after venous valve lysis. To record the serial venous pressure data at the three chronic postlysis intervals, the dogs were again sedated and anesthetized as described above.

In the development of this model, a number of pilot animals were used to test various techniques for the creation of valve incompetence. A retrograde perfusion system for the Leather valve cutter was employed (identical to its arterial application for in situ bypass grafts) but was too cumbersome to pass through the valved side branches of the canine iliac or common femoral veins. Rigid metal valvulotomes, such as the 2.0-mm and 2.5-mm Hall (Solco-Basle, Inc, Rockland, Mass) and the 2.0-mm and 3.0-mm LeMaitre (Vascutech, Andover, Mass), were tested, but the former consistently caught on branch points and lacerated the vein and the latter were unable to render valves incompetent. We also tested the 3.0-mm Leather valve cutter, but this was too large to pass easily through the lateral saphenous vein and only inconsistently caused valve incompetence (one of the 13 dogs described herein had the 3.0-mm cutter unsuccessfully passed before the successful use of the 2.0-mm cutter). In two dogs (also described in this study), ligation of the medial saphenous vein and the popliteal vein (which is a diminutive vessel in the dog) was added to augment the venous insufficiency caused by the 2-mm Leather-valve cutter; however, compared with valve lysis alone, this resulted in no enhancement of venous insufficiency over time.

Venographic and Pathologic Analysis

In six dogs, descending venograms were obtained with the dogs in the 80° semierect position. An injection of 50 mL at 10 mL/s of diatrizoate meglumine (Hypaque 60, Winthrop, New York, NY) was

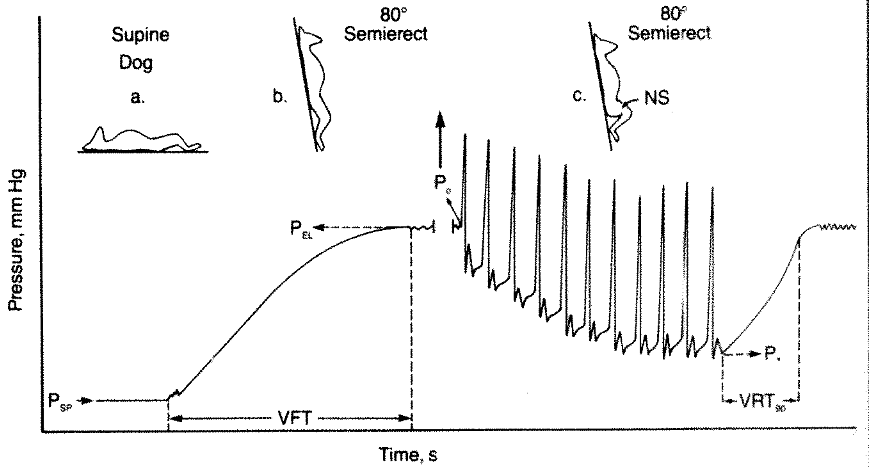

Fig 3.—Schematic representation of a typical pressure recording. Diagram shows supine position at rest (a), venous filling with elevation (b), and muscle stimulation to empty hindlimb veins (c). P_{SP} indicates supine pressure; P_{EL}, elevation pressure; VFT, venous filling time; P_o, prestimulus pressure; P., poststimulation venous pressure; VRT_{90}, 90% venous refilling time; and NS, nerve stimulator.

administered via a catheter passed percutaneously through the external jugular vein and positioned in the external iliac vein on the left side. In three of these dogs, a descending venogram of the right (control) hindlimb was similarly obtained.

In eight dogs (including the six with venograms), at the time of killing, the competency of the midsuperficial femoral vein valve (below entry of the profunda femoral vein) was determined by use of the manual strip test.[4]

Statistical Analysis

The mean and SEM were computed for the two sets (left experimental valve lysis limb and right control limb) of six measured hemodynamic variables: supine pressure (P_{SP}), elevation pressure (P_{EL}), VFT, P_o, P., *and* VRT_{90} at the five time intervals measured (T1 through T5). Three-way analysis of variance with repeated measures (dog, treatment, *and* time) was used to determine overall significance of differences for each of the six hemodynamic variables. Mean pairwise differences between experimental and control limbs at T1 through T5 were determined by paired *t* tests. To determine the sensitivity (true-positive/[true-positive + false-negative]) of the hemodynamic variables in discrimination of valvular incompetence with this model, we selected as "true-positive, abnormal values" those that gave a 95% specificity based on a frequency distribution of the normal values (normal defined as left limb measurements at T1 and right limb measurements at T1 through T5, all of which represent nonlysed valves).

RESULTS

For the six measured variables in the experimental limb (left) at baseline before valve lysis (T1), the values were as follows: P_{SP}, 8.1 ± 1.25 mm Hg; P_{EL}, 52.8 ± 1.30 mm Hg; VFT, 18.0 ± 3.20 seconds; P_o, 52.4 ± 1.20 mm Hg; P., 27.6 ± 1.68 mm Hg; and VRT_{90}, 1.6 ± 0.44 seconds. These values were not significantly different from the control (right) limb values at T1, and no significant change from baseline was noted in the control limb during the subsequent period of observation (T2 through T5).

The P_{SP} of the left limb immediately after valve lysis (T2) was significantly elevated compared with that of the control right limb (14.7 ± 1.74 vs 9.8 ± 1.38 mm Hg, $P<.05$) but thereafter returned to baseline levels for the remainder of the experiment. For both P_{EL} and P_o, no significant differences were noted between limbs at any time either before or after valve lysis (T1 through T5).

Immediately after valve lysis (T2), VFT was shortened compared with that of the control limb (6.2 ± 1.09 vs 28.0 ± 5.72 seconds, $P<.005$) and remained significantly ($P<.025$) shorter at T3 through T5 (Fig 4). Valve lysis also resulted in an elevated P. at T2 compared with the control limb (46.5 ± 1.46 vs 26.2 ± 1.45 mm Hg, $P<.0001$), with this difference persisting at T3 through T5 ($P<.005$, Fig 4). Finally, at T2, VRT_{90} was significantly more rapid in the limb in which valve lysis was performed (0.2 ± 0.04 vs 3.0 ± 0.44 seconds, $P<.0001$), and this difference from control was maintained at T3 through T5 ($P<.01$, Fig 4).

The individual animal data for VFT, P., and VRT_{90} were plotted to qualitatively assess the variability among dogs and within the same dog over time (Fig 5). The sensitivities of VFT, P., and VRT_{90} and the values from which these were derived for 95% specificity (given parenthetically) were as follows: VFT, 75% (<7.2 seconds); P., 89% (>38 mm Hg); and VRT_{90}, 100% (<0.6 seconds).

In eight of eight dogs, the strip test[4] confirmed incompetence of the lysed midsuperficial femoral vein valve; in all six of these dogs in which descending venograms were obtained, the veins were patent without apparent scarring and there was reflux into the lateral saphenous vein below the knee. In three of three dogs, contrast material refluxed to the same extent in the control, nonlysed limb as in the lysed, hemodynamically insufficient limb.

In all 13 dogs with chronic venous valvular insufficiency, no wound dehiscence or infection, persistent edema, ulcers, or pain was observed. Due to repeated catheterization, thrombosis occurred in the most caudad segments of the lateral saphenous vein at the ankle; however, in only one dog did this progress to the infrageniculate popliteal fossa, requiring killing of the dog at 3 weeks to obtain pressure measurements after deep dissection for cannulation of the lateral saphenous vein; this precluded further serial venous pressure measurements (with no measurement at T3; hence, n = 12).

COMMENT

The most widely applicable, and currently the most effective, method of direct venous reconstruction for deep venous insufficiency is insertion of a competent valve.[5] The clinical feasibility of such surgery was first confirmed by Taheri and associates[6] with their report of autogenous brachial-to-femoral vein valve transplantation.

Previous models of valve incompetence have been used to develop valve transplantation techniques. In 1965, McLachlin and associates[7] created a canine model simulating postphlebitic deep venous incompetence with the use of mechanical trauma and stasis to cause thrombosis and recanalization of

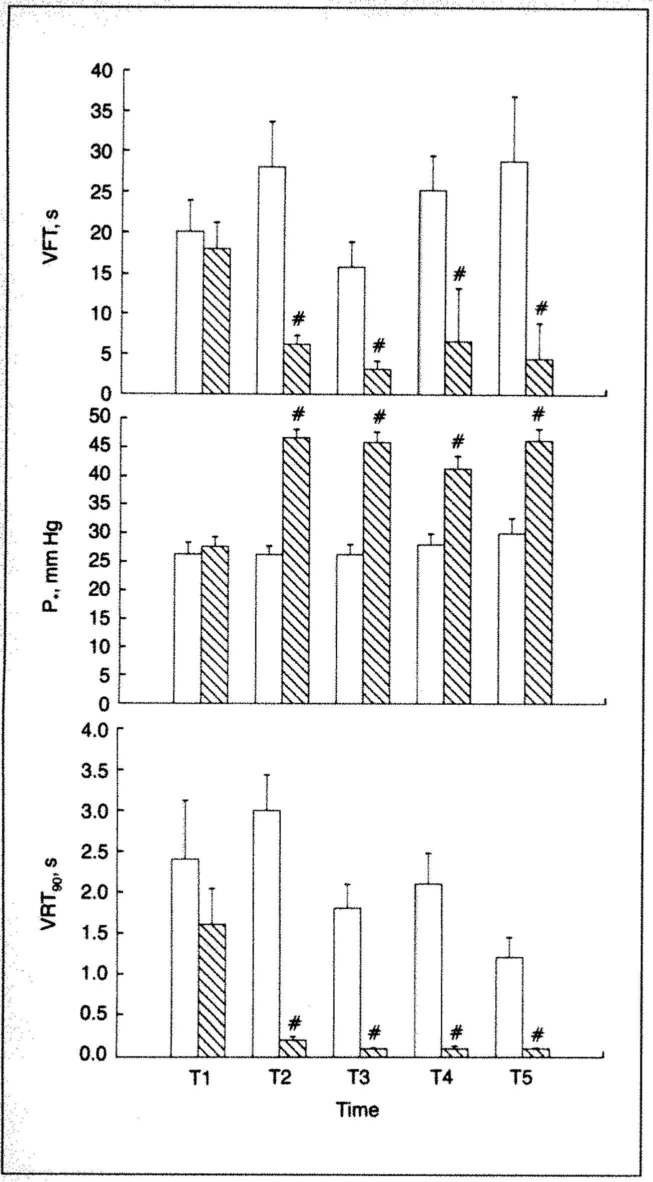

Fig 4.—Paired comparison of control (open bars) and experimental (hatched bars) hindlimbs at baseline (T1), immediately after valve lysis (T2), and 1 to 2 weeks (T3), 3 to 5 weeks (T4), and 9 to 14 weeks (T5) after lysis. VFT indicates passive venous filling time; P., poststimulation venous pressure; VRT$_{90}$, 90% venous refilling time; and number symbol, significant difference in paired comparisons at each time interval for each variable ($P<.025$).

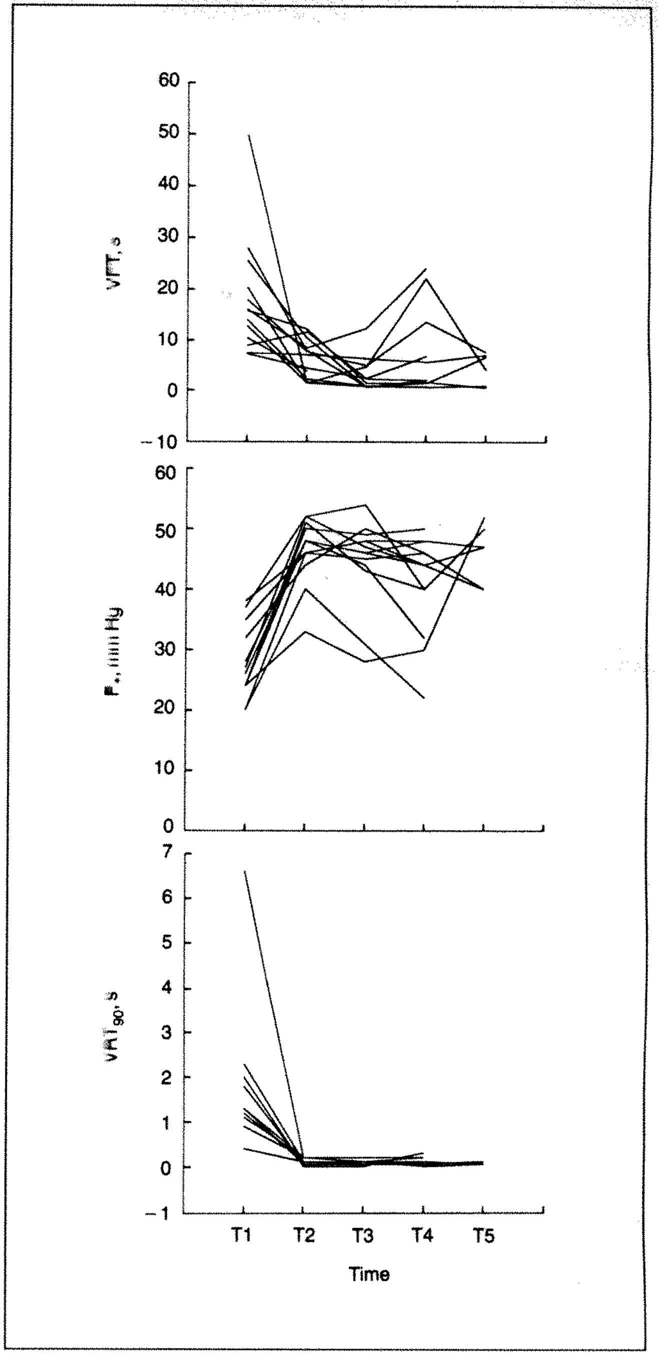

Fig 5.—Plots of individual dog data measured over the five time intervals for the three variables that are discriminatory for valve incompetence. VFT indicates venous filling time; P., poststimulation venous pressure; and VRT$_{90}$, 90% venous refilling time.

the superficial femoral vein for subsequent valve transplantation experiments. Vein clamping was required for 48 to 96 hours to induce thrombosis, and the time required for recanalization ranged from 19 to 56 days. In 1967, Waddell and associates[8] used both the mechanical trauma/stasis method and phlebitis induced with the sclerosant monoethanolamine to create venous valve incompetence. The clamp-occlusion method had an 83% success rate in the production of a model for valve transplantation, but required 2 to 5 weeks for recanalization and was associated with a 14% attrition rate due to death or wound complications that prohibited venous reconstruction. The chemically induced phlebitis technique resulted in thrombosis in only 90% of dogs, with recanalization in only 78% of these after 6 to 11 weeks; among the recanalized veins, 57% were unusable for valve transplant experiments due to densely adherent partial recanalization. Neither group of authors[7,8] reported hemodynamic proof of venous insufficiency in their animals.

More recently, van Bemmelen et al[9] developed an experimental model of venous valve insufficiency in rats by subjecting valves to hemodynamic stress from cephalad femoral arteriovenous fistulas. Their method was associated with 25% mortality due to congestive heart failure. Jessup and Lane[10] applied the same technique in a sheep model. In addition to the labor-intensive step required to create the arteriovenous fistula, this was a model not of phlebitic damage to valve cusps but rather of valve incompetence caused by initial vein dilatation and separation of the commissures.[10] Again, no hemodynamic evidence of venous insufficiency was reported by either group.[9,10]

Our valve lysis method was technically simple, quick, reproducible, and stable up to 14 weeks, with all dogs having hemodynamically verified venous insufficiency at the time of killing. Descending venography was useful in the demonstration of patent, nonrecanalized, incompetent veins in our study; however, this method was cumbersome, invasive, and nonspecific, as in three of three normal nonlysed limbs, contrast material refluxed to the same degree as in the lysed limb despite hemodynamic evidence of venous insufficiency only in the latter. Discrepancy between venographic and actual strip test assessment of valve function has been documented previously.[11] We developed this valvular insufficiency model for future tests of venous valve reconstructive procedures. Rather than use venographic quantitation of reflux, we concentrated on the development of functional hemodynamic tests, as there is an acknowledged need for such assessments of total limb venous dynamics for critical evaluation of venous reconstructive procedures.[1]

The fact that there was no external evidence of venous insufficiency (edema or ulcers) is not surprising given the relatively short-term nature of the study and the short hydrostatic column in an animal who walks on all four extremities. It is not unusual for patients with venous valvular insufficiency documented by venography and noninvasive tests to display no external sequelae for years. In terms of an animal model for surgical experimentation, it is the hemodynamic verification of valvular insufficiency that is important for the assessment of the efficacy of valve transplants.

Among the six hemodynamic variables measured, only VFT, P_o, and VRT_{90} were discriminatory for valvular insufficiency. Supine resting pressure was significantly elevated only at T2, consistent with venospasm resulting from repeatedly passing the valve cutter in the experimental limb. Otherwise, P_{SP} and the resting semierect pressures, P_{EL} and P_o, were not altered by valve lysis, an expected result given the fact that these three variables measure resting venous capacitance and are a reflection of the effects of arterial inflow and gravity rather than a function of venous valve competence.

Although VFT and P_o were significantly different after valve lysis, indicating venous reflux and inadequate venous emptying, these tests were relatively insensitive (75% and 89%, respectively). However, VRT_{90} was 100% sensitive if a value less than 0.6 seconds was measured. This would be expected because, among the six variables, VRT_{90} is the most physiologic measure of valvular insufficiency due to the fact that it measures venous refilling after maximum emptying of the venous system with an active hindlimb muscle pump. We conclude that for future applications of this canine model of valvular insufficiency, a VRT_{90} of less than 0.6 seconds is the objective hemodynamic standard that confirms incompetence of venous valves.

In contrast to past models of valvular insufficiency, our valve lysis method damages the valve cusps directly, simulating the postphlebitic situation, but avoids disturbance of the deep venous system by surgical manipulation. Thus, subsequent experimental deep venous valve reconstructive surgery would be facilitated. The successful development of an upright, large-animal model of venous valvular insufficiency that can be verified by functional tests of hindlimb venous hemodynamics should allow evaluation of valve replacement procedures that will have clinical application.

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The Dichotomous Distribution of Gastrinomas

Mark P. Sawicki, MD; Thomas J. Howard, MD; Marci Dalton; Bruce E. Stabile, MD; Edward Passaro, Jr, MD

• Our experience with 47 sporadic gastrinomas suggests that no less than 85% of these tumors are located to the right of the superior mesenteric artery. This finding is unexpected because approximately 75% of insulinomas and glucagonomas are located to the left of the superior mesenteric artery. All of our extrapancreatic gastrinomas have been located to the right. These observations prompted us to determine if other extrapancreatic gastrinomas were also predominantly located to the right side. We searched the world's literature and found 10 cases of ovarian gastrinomas and one case of a renal gastrinoma. Nine of these remote extrapancreatic gastrinomas were located on the right side. This distribution of remote extrapancreatic gastrinomas is similar to our experience with peripancreatic gastrinomas. This unexpected right-sided preponderance of both remote and peripancreatic gastrinomas suggests a common origin for both.

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Currently it is thought that pancreatic islets arise from immature endocrine precursor cells situated in the epithelium of the developing pancreatic acinar ducts.[1] One of the theories of pancreatic endocrine tumor development postulates that they arise from these totipotential precursor cells.[2] The other theory states that these tumors derive from more differentiated islet cells. If development of pancreatic endocrine tumors was a random event occurring in totipotential cells, it would be expected that the incidence of these tumors would be similar in all portions of the pancreas. Our observation, however, has been that these tumors are not evenly distributed.

A recent study using the superior mesenteric artery as a landmark demonstrated that pancreatic endocrine tumors are not uniformly distributed.[3] Gastrinomas arise predominantly on the right side of the vessel whereas insulinomas, for example, arise predominantly on the left. At least 30% of the gastrinomas that are found to the right of the mesenteric artery are not in the pancreas itself but are extrapancreatic (Table 1).[3,4] None of the extrapancreatic gastrinomas, however, are found to the left of the superior mesenteric artery. These extrapancreatic gastrinomas have been found chiefly adjacent to the pancreas and rarely at distant sites.

More remote extrapancreatic gastrinomas have been reported to occur in lymph nodes, duodenum, ovary, kidney, mesentery, omentum, stomach, and liver.[5] While it has been demonstrated that peripancreatic gastrinomas are predominantly found to the right of the superior mesenteric artery, the anatomic distribution of remote extrapancreatic gastrinomas is not known.

The goal of this study was to determine if the right and left distribution of remote extrapancreatic gastrinomas was similar to or different from that of peripancreatic gastrinomas. In particular, we focused on two remote sites for gastrinoma in which the issue of bilaterality could be addressed, namely, the kidneys and ovaries.

METHODS

We searched the world's literature using the National Library of Medicine database from 1968 through 1989. We searched both titles and abstracts and used the following key words: gastrinoma, Zollinger-Ellison syndrome, ovary, and kidney. We reviewed all of the articles in all languages and present the data herein. The data were analyzed for statistical significance using the binomial expansion assuming a 50/50 right and left distribution.[6]

RESULTS

We found 11 cases of renal and ovarian tumors causing Zollinger-Ellison syndrome (Tables 2 and 3).[7-18] Ovarian gastrinomas were present in 10 patients and a renal gastrinoma was present in one. In all cases, the tumor was confined to the kidney or ovary and was unilateral.

Most of these patients presented with the following symptoms of Zollinger-Ellison syndrome: abdominal pain (11 of 11 patients), diarrhea (five of 11 patients), duodenal obstruction (one of 11 patients), perforation (one of 11 patients), and bleeding (three of 11 patients). None of the patients had a family history consistent with multiple endocrine neoplasia type I syndrome. Normal serum prolactin levels were reported in six of 11 patients. Endoscopic or barium studies of the upper gastrointestinal tract uniformly revealed active ulcer disease. Fasting serum gastrin levels were elevated and ranged from 530 to 5800 ng/L. Secretin or calcium infusion tests were performed in eight patients and were positive in six. Imaging studies, including computed tomographic scan, ultrasound, and angiography, were able to identify the tumor in five of the six patients from whom such studies were obtained.

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Read before the 14th Annual Surgical Symposium of the Association of Veterans Affairs Surgeons, Charleston, SC, May 8, 1990.

Reprints not available.

Every patient underwent exploratory laparotomy and excision of the gastrinoma. At operation, eight of 10 ovarian tumors and the one renal tumor were present on the right side ($P = .03$). Thorough surgical exploration of the pancreas and duodenum failed to reveal other tumors. Patients with ovarian tumors underwent salpingo-oophorectomy (five of 10 patients), bilateral salpingo-oophorectomy (five of 10 patients), and total abdominal hysterectomy (four of 10 patients). Acid-reducing operations were performed in four patients: vagotomy and pyloroplasty (one patient), highly selective vagotomy (two patients), and total gastrectomy (one patient). The patient with a renal tumor underwent right nephrectomy. No acid-reducing operations were performed in this group. After operation, the serum gastrin levels returned to normal. Those patients with abnormal secretin levels had a return to normal levels. Those patients who had abnormal secretin levels preoperatively had normal levels postoperatively (follow-up, 2 to 72 months).

Table 1.—Gastrinoma Distribution

	SMA*	
	Right	Left
Pancreatic	32	4
Peripancreatic	11	0
Remote		
Ovary	8	2
Renal	1	0

*SMA indicates superior mesenteric artery.

All of the ovarian tumors were large, cystic, and multiloculated. They were confined to the ovary except in one case in which a single lymph node metastasis was found.[8] The histologic appearance of the ovarian tumors was similar in all. The tumors were classified as either mucinous cystadenocarcinomas or mucinous cystadenomas and none were consistent with the carcinoid type. Solid masses of tumors were not seen. The cysts were lined by columnar or pseudostratified columnar epithelium. All of the tumors stained positively for gastrin except for one in which the tumor was assayed for gastrin but

Table 2.—Clinical Data*

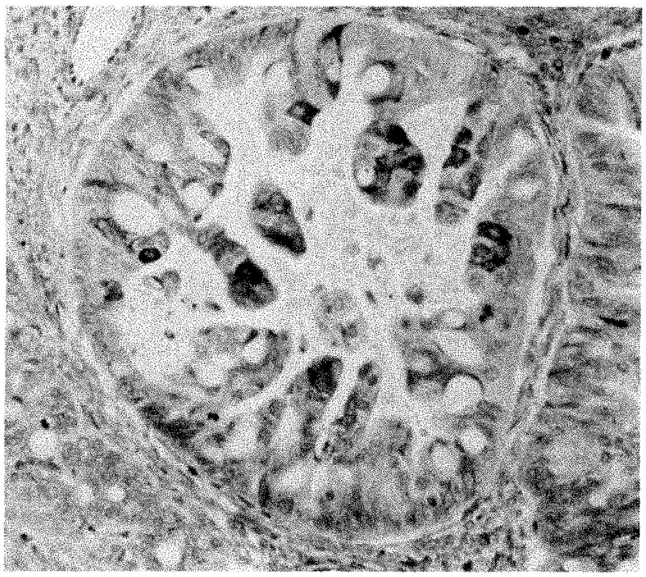
Age, y/Sex	Duration of Symptoms, mo	Basal Gastrin, ng/L	Secretin/Calcium		Follow-up, mo	Source
			Preoperative	Postoperative		
76/F	6	2117	ND	N	72	Alder and Rossler[6]
47/F	"Recent"	1500-5800	A	N	2	Garcia-Villanueva et al[7]
53/F	4	731-908	A	N	12	Heyd et at[8]
35/F	ND	980-1175	A	ND	24	Maton et al[9]
60/F	12	750	N	ND	12	DeBroucker et al[10]
35/F	3	680-940	N	ND	42	Primrose et al[11]
37/F	9	444	ND	ND	ND	Morgan et al[12]
51/F	3	750-1170	ND	N	9	Julkunen et al[13]
49/F	"Several"	350-530	A	N	18	Bollen et al[14]
62/F	12	2456	A	ND	6	Long et al[15]
12/M	6	4764	A	N	6	Cocco and Conway[16]

*A indicates abnormal; N, normal; and ND, no data.

Table 3.—Clinical Data*

Operation	Gross	Microscopic	Immunohistochemistry	Source
TAH/BSO	L ovary, multiloculated, 16 × 12 × 6 cm, 1100 g	Mucinous cystadenocarcinoma	+ Gas, − PP, − Sec	Alder and Rossler[6]
TAH/BSO	R ovary, multiloculated, 35 × 35 × 35 cm, 1100 g	Cystadenocarcinoma metastatic to LN, heterotopic pancreas in jejunum	+ Gas	Garcia-Villanueva et al[7]
BSO	R ovary, multiloculated, 25 × 20 × 12 cm	Mucinous cystadenocarcinoma	+ Gas	Heyd et al[8]
V&P/RSO	R ovary, multiloculated, 16 × 10 × 9 cm	Mucinous cystadenoma	+ Gas, + SS	Maton et al[9]
TAH/BSO	R ovary, multiloculated, 22 × 19 × 10 cm, 2505 g	Mucinous cystadenoma	+ Gas	deBroucker et al[10]
HSV/RSO, gastrojejunostomy, duodenoduodenostomy	R ovary, multiloculated, 30 × 11 × 9 cm, 700 g	Mucinous cystadenocarcinoma	+ Gas, + SS, − PP, − GLU	Primrose et al[11]
RSO	R ovary, multiloculated, 7000 g	Mucinous cystadenoma	+ Gas	Morgan et al[12]
HSV/RSO	R ovary, multiloculated, 14 × 14 × 8 cm	Cystadenocarcinoma, borderline malignant	+ Gas	Julkunen et al[13]
TAH/BSO	R ovary, multiloculated, 10 × 12 × 12 cm	Mucinous cystadenoma	+ Gas	Bollen et al[14]
TG/LSO	L ovary, multiloculated, 16 × 10 × 9 cm	Mucinous cystadenoma	Not done	Long et al[15]
Nephrectomy	R kidney, solid mass, 3 × 3 × 2 cm	Islet cell tumor	+ Gas, + ChromA, − SS, − PP, − Glu, − Ins	Cocco and Conway[16]

*TAH indicates total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LSO, left salpingo-oophorectomy; RSO, right salpingo-oophorectomy; HSV, highly selective vagotomy; Gas, gastrin; SS, somatostatin; Sec, secretin; Ins, insulin; Glu, glucagon; PP, pancreatic polypeptide; ChromA, Chromogranin A; V&P, vagotomy and pyloroplasty; TG, total gastrectomy; LN, lymph node; plus sign, stains for hormone; and minus sign, does not stain for hormone by immunodiffusion.



Immunoperoxidase staining for gastrin in an ovarian tumor counterstained with hematoxylin (from Heyd et al[8]).

immunohistochemistry studies were not performed. Typically, numerous gastrin-staining cells lined the cysts (Figure). In one case, the basal portion of the cells stained for gastrin whereas the apical portions of the cells stained for mucin.[8] Immunohistochemistry studies for other substances were done in three cases. Somatostatin was the only other peptide identified. Pancreatic polypeptide was absent.

The renal tumor was much smaller compared with the ovarian tumors. The histologic appearance more resembled that of typical gastrinomas in that the gastrin-staining cells were confined to a discrete mass. Immunoperoxidase staining was positive for gastrin.

COMMENT

In our study, nine of 11 patients had ectopic ovarian or renal gastrinomas located to the right of the superior mesenteric artery ($P = .03$). Our experience with 47 sporadic gastrinomas suggests that extrapancreatic gastrinomas are found to the right of the superior mesenteric artery.[4] Taken together, these findings support our hypothesis that these two groups, peripancreatic and remote gastrinomas, have a similar right and left distribution and may have been caused by the same mechanism.

The presence of peptides in mucinous tumors of the ovary is well known.[18-20] A variety of peptides may be demonstrated, including gastrin, pancreatic polypeptide, serotonin, somatostatin, neurotensin, adrenocorticotropin, glucagon, and calcitonin. In a study of 47 unselected mucinous ovarian tumors, 14 stained positively for gastrin.[18] Despite the high number of gastrin-staining tumors, none of these patients had clinical evidence of Zollinger-Ellison syndrome.

One of the theories of pancreatic endocrine tumor development postulates that they are derived from immature endocrine precursor cells in the developing pancreatic ducts.[2] These totipotential cells then differentiate into cells capable of elaborating islet peptides. This theory implies that tumor development occurs as a random event in endocrine precursor cells, resulting in a uniform distribution of these tumors within the pancreas.

This paradigm was challenged recently when it was demonstrated that pancreatic endocrine tumors have a heterogeneous distribution.[3] In a collective review of the literature, Howard et al[3] found that the anatomic distribution of pancreatic endocrine tumors fell into two clusters. Cluster 1 consisted of gastrinomas, pancreatic polypeptide-secreting tumors, and somatostatinomas and had 75% of tumors located to the right of the superior mesenteric artery, and cluster 2 consisted of insulinomas and glucagonomas and had 75% of tumors located to the left of the superior mesenteric artery. These findings, with the exception of somatostatinomas, are consistent with the known distribution of pancreatic islet endocrine cell types that are not uniform in either their distribution or cellular composition. These data suggest that at least some of these tumors arise from more differentiated cells rather than from totipotential cells.

The right-sided preponderance of mucinous tumors of the ovary causing the Zollinger-Ellison syndrome is unexpected. Mucinous tumors of the ovary occur with equal frequency in the right and left ovaries.[21] It would be expected, therefore, that ovarian tumors causing Zollinger-Ellison syndrome would occur with equal frequency in the right and left ovaries. This right-sided preponderance is also in disagreement with the current theories of oncogenesis of mucinous tumors of the ovary.

The exact oncogenesis of mucinous tumors of the ovary is not known. Two theories have gained acceptance.[18] According to the surface epithelial metaplasia theory, coelomic epithelium proliferates during ovulation and develops an inclusion that later transforms into an endocervical type of neoplastic tissue. This tissue then undergoes metaplasia to form intestinal epithelium. The second theory is that some of these tumors are of germ cell origin with differentiation into an endodermal type of epithelium.

Neither of these theories, however, would explain the right-sided preponderance of mucinous tumors causing Zollinger-Ellison syndrome. This suggests that the oncogenesis of these gastrin-secreting tumors is different from other mucinous tumors of the ovary and more resemble their peripancreatic counterparts.

In our study, nine of 11 gastrin-secreting ovarian and renal tumors were located to the right of the superior mesenteric artery ($P<.05$). Currently, there is no explanation for this right-sided preponderance. These observations may be an important clue in determining the origin of gastrinomas.

P. Maton, R. Jensen, and S. Mackem at the National Institutes of Health, Bethesda, Md, provided the photomicrograph of the immunoperoxidase-stained ovarian gastrinoma used as the Figure in this article.

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Invited Commentary

The authors have previously documented for us, in a clear fashion, that pancreatic islet cell tumors may anatomically be neatly divided into either cluster 1 (gastrinomas, pancreatic polypeptide-secreting tumors, and somatostatinomas) or cluster 2 (insulinomas, glucagonomas) groups. The fact that ±80% of cluster 1 tumors occur to the right and ±80% of cluster 2 tumors occur to the left of the superior mesenteric artery has been well substantiated by many authorities in this field, and this distribution is believed to correspond closely to the volume density of the endocrine-secreting cells of the pancreas with a notable exception being that of the delta cells (somatostatinomas).

The current study reports a predominance of right-sided, extrapancreatic gastrinomas; based on this finding, the authors question the embryologic origin of pancreatic islet cells. This question is a most appropriate one, for much has changed in the 50 years since Feyrter first proposed a diffuse endocrine system—a proposal that gained in popularity because of the contribution of Pearse in 1966 who coined the now popular term *APUD-omas* (amine precursor uptake and decarboxylation). The postulate was that all of these cell types (±40) arose from the primitive neural crest and were thus of neuroectodermal origin. This embryologic package was, perhaps, "too neat" to be true.

Using embryologic cell-tracing methodology and transgenic mice to study vertebrate development, it is now abundantly clear that the origin of the endocrine cells of the pancreas and of the gastrointestinal tract that secrete neuropeptide or polypeptide hormones is not of neural crest origin. Researchers have demonstrated the development of gut enterochromaffin cells after the removal of gut tissue prior to neural crest formations. Similarly, tumors such as fibrosarcomas and patients with myeloblastic leukemia have been shown to secrete insulin and corticotropin, respectively, strongly suggesting an endodermal or mesodermal origin.

The current opinion is that the islet cells of the pancreas are of endodermal origin. However, the possibility of a common "ectoblastic precursor cell" that becomes incorporated into the developing endoderm that may later differentiate into the endocrine cells of the pancreas cannot be excluded.

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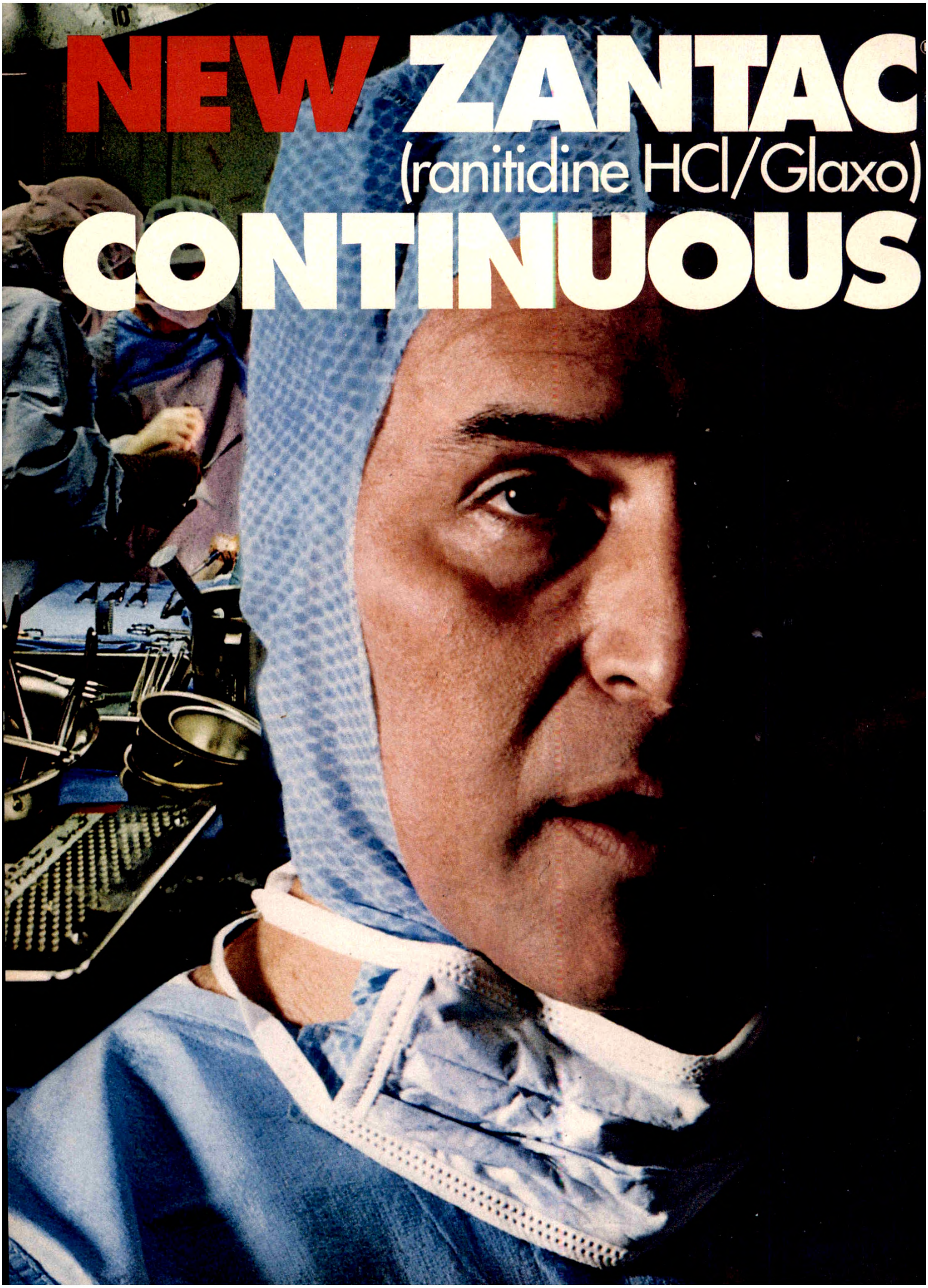
Rochester, Minn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* Please see complete Prescribing Information for indications.

† Rare cases of CNS effects, usually reversible, have been reported. Please see complete Prescribing Information for precautions.

Please see references and Brief Summary of Prescribing Information on next page.

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Zantac* Injection
(ranitidine hydrochloride)

BRIEF SUMMARY

Zantac* Injection Premixed
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac* Injection/Zantac* Injection Premixed product labeling.

INDICATIONS AND USAGE: Zantac* Injection and Zantac* Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.

CONTRAINDICATIONS: Zantac* Injection and Zantac* Injection Premixed are contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac* therapy does not preclude the presence of gastric malignancy.

2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended doses for five days or longer. Therefore, it seems prudent in patients receiving intravenous (IV) ranitidine at doses greater than or equal to 100 mg qid for periods of five days or longer to monitor SGPT daily (from day 5) for the remainder of IV therapy.

4. Bradycardia in association with rapid administration of Zantac* Injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded (see DOSAGE AND ADMINISTRATION).

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at oral doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at oral doses up to 160 times the human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) treated with oral Zantac were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: Transient pain at the site of intramuscular injection has been reported. Transient local burning or itching has been reported with IV administration of Zantac*.

The following have been reported as events in clinical trials or in the routine management of patients treated with oral or parenteral Zantac. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, asystole, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac* Injection/Zantac* Injection Premixed product labeling.)

Intramuscular Injection: 50 mg (2 ml) every six to eight hours. (No dilution necessary.)

Intermittent Intravenous Injection:

a. Intermittent Bolus: 50 mg (2 ml) every six to eight hours. Dilute Zantac Injection, 50 mg, in 0.9% Sodium Chloride or other compatible IV solution (see Stability) to a concentration no greater than 2.5 mg/ml (20 ml). Inject at a rate no greater than 4 ml per minute (five minutes).

b. Intermittent Infusion: 50 mg (2 ml) every six to eight hours. Dilute Zantac Injection, 50 mg, in 5% Dextrose Injection or other compatible IV solution to a concentration no greater than 0.5 mg/ml (100 ml). Infuse at a rate no greater than 5 to 7 ml per minute (15 to 20 minutes).

Zantac Injection Premixed solution, 50 mg, in 0.45% Sodium Chloride, 100 ml, requires no dilution and should be infused over 15 to 20 minutes.

In some patients it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of the dose, but generally should not exceed 400 mg per day.

Continuous Intravenous Infusion: Add Zantac Injection to 5% Dextrose Injection or other compatible IV solution. Deliver at a rate of 6.25 mg per hour (eg, 150 mg [6 ml] Zantac Injection in 250 ml of 5% Dextrose Injection at 10.7 ml per hour).

For Zollinger-Ellison patients, dilute Zantac Injection in 5% Dextrose Injection or other compatible intravenous solution to a concentration no greater than 2.5 mg/ml. Start the infusion at a rate of 1.0 mg/kg/h. If after four hours either a measured gastric acid output is greater than 10 mEq/h or the patient becomes symptomatic, the dose should be adjusted upwards in 0.5-mg/kg/h increments, and the acid output should be remeasured. Doses up to 2.5 mg/kg/h and infusion rates as high as 220 mg/h have been used.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 50 mg every 18 to 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac* Injection, 25 mg/ml, containing phenol 0.5% as preservative, is available as follows:
NDC 0173-0362-38 2-ml single-dose vials (Tray of 10)
NDC 0173-0363-39 10-ml multi-dose vials (Singles)
NDC 0173-0363-00 40-ml Pharmacy Bulk Packages (Singles)
NDC 0173-0362-00 2-ml single-dose, prefilled, disposable syringes (Singles)

Store below 30° C (86° F). Protect from light. Store 40-ml vial in carton until time of use.

Zantac* Injection Premixed in 0.45% Sodium Chloride, 0.5 mg/ml, is available as a sterile, premixed solution for IV administration in 100-ml, single-dose, flexible plastic containers (NDC 0173-0407-00). It contains no preservatives.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25° C); however, brief exposure up to 40° C does not adversely affect the product.

August 1990

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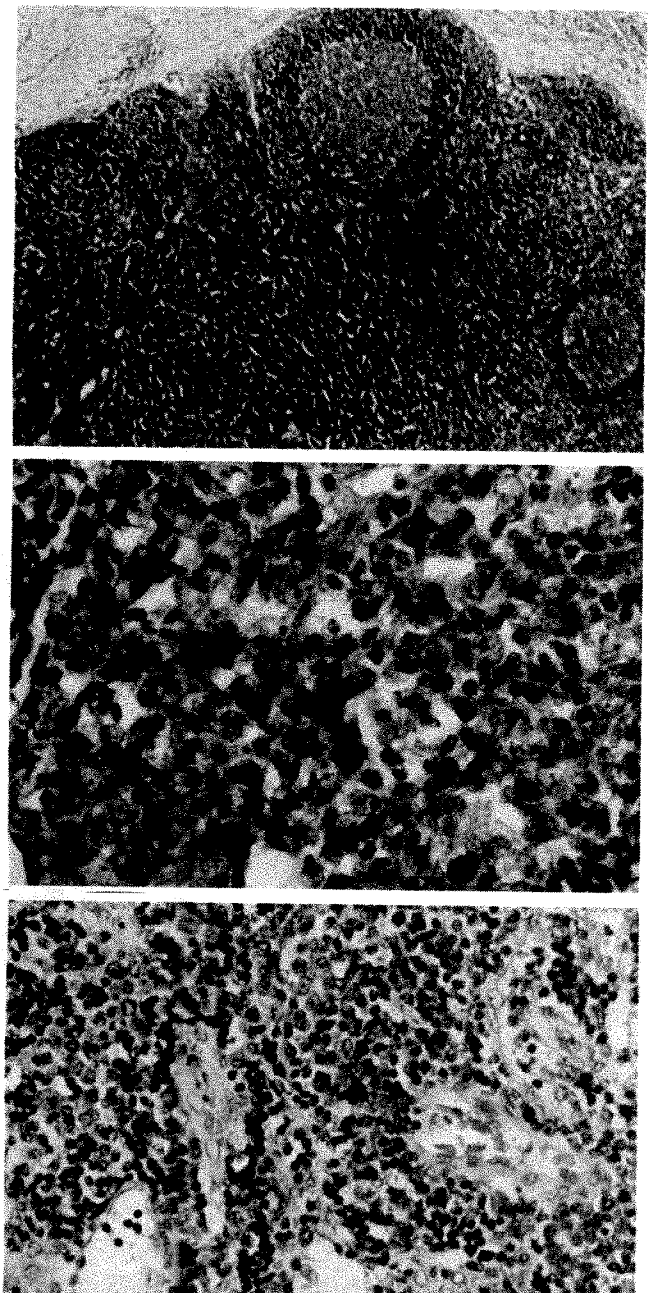
recorded, including the percentage of stained cells and the intensity of staining.

RESULTS

The effect of the location of lymph nodes on fusion frequency and the yield of antigen-reactive clones was first studied. Lymphocytes from three lymph nodes (A1 to A3) of a single patient were fused with SHFP-1 cells without IVI. Results showed that lymphocytes of cancer patients were capable of forming tumor-reactive HuMAbs, although the yield of tumor-reactive clones was at the rate of 1 per 1×10^7 to 1 per 1×10^8 cells. The lymph node (A1) closest to the tumor mass gave the best yield in both fusion frequency and tumor-reactive clones (Table 1). Histologic evaluation of all three lymph nodes showed that A1 had the most significant hyperplastic changes in all areas, including the germinal center, paracortical area, and medulla, with increased number of lymphoblasts and plasma cells (Fig 1). With IVI, including sPWM-T as the B lymphocyte stimulant and CEA as the antigen, the fusion frequency was increased by 4.5 to 31.5 times compared with the non-IVI protocol. In addition, the number of HT-29 tumor-reactive clones was significantly increased when the IVI procedure was used on lymphocytes from cancer patients (up to 13.6 times). Most of the stable HT-29 tumor-reactive clones were derived from the fusions with IVI protocols. When CEA was the antigen used in the IVI protocol, HT-29 tumor-reactive clones were obtained in both CEA- and non-CEA–related fashions. No CEA-reactive clones were produced by the non-IVI protocol (Table 1).

Fig 1.—Hyperplastic lymph node obtained from a patient with Dukes' A colon cancer. Top, Hyperplastic change at the germinal center and in the paracortical area (immunoperoxidase, original magnification ×250). Center, Increased number of lymphoblasts at the medulla (immunoperoxidase, original magnification ×400). Bottom, Increased number of plasma cells at the medulla (immunoperoxidase, original magnification ×400).



In addition, the IVI protocol increased the immunoglobulin secretion of all isotypes. With the IVI protocol, IgG- or IgA-secreting clones were obtained approximately 10 times more frequently than with the non-IVI control (Table 2). Increased isotype switching by IVI may improve the probability of obtaining HT-29 tumor-reactive, IgG-secreting clones.

To search for the optimal stimulant for B cells in IVI, sPWM-T and sMLC were compared. We used CEA at 20 μg/L as the immunogen in this experiment. To avoid unnecessary experimental variations that might have affected the results, all six IVI experiments were performed simultaneously (Table 1). Although both B-cell–stimulating conditioning media enhanced the fusion frequency, there was no improvement in the yield of HT-29 tumor-reactive clones using sMLC compared with the non-IVI control. Only one HT-29 tumor-reactive clone resulted from sMLC stimulation. In contrast, sPWM-T stimulated significantly more HT-29 tumor-reactive clones. In vitro immunization with sPWM-T demonstrated more frequent hybridoma formation with a shorter delay after fusion than the IVI protocol with sMLC (Fig 2). Positive hybridomas developing soon after fusion seemed more stable than those requiring prolonged incubation. As a stimulant to human B lymphocytes, sPWM-T appeared to be superior to sMLC.

During our initial IVI studies, CEA at 20 μg/L was chosen for the following reasons: (1) Carcinoembryonic antigen is

Table 2.—Isotypes of Human Monoclonal Antibodies Derived From IVI and Non-IVI Protocols*

Lymph Node	Protocol	Immunoglobulin Isotype, %†		
		IgM	IgG	IgA
A1	IVI with sPWM-T	41.3	3.8	10.0
	Non-IVI	10.4	0.6	1.0
A2	IVI with sPWM-T	26.6	7.3	8.9
	Non-IVI	8.2	1.7	0
A3	IVI with sPWM-T	70.0	5.8	6.7
	Non-IVI	2.4	0.4	0

*IVI indicates in vitro immunization; sPWM-T, supernatant of pokeweed mitogen–stimulated T lymphocytes.

†[(No. of specific isotype-secreting clones)/(No. of wells plated)] × 100.

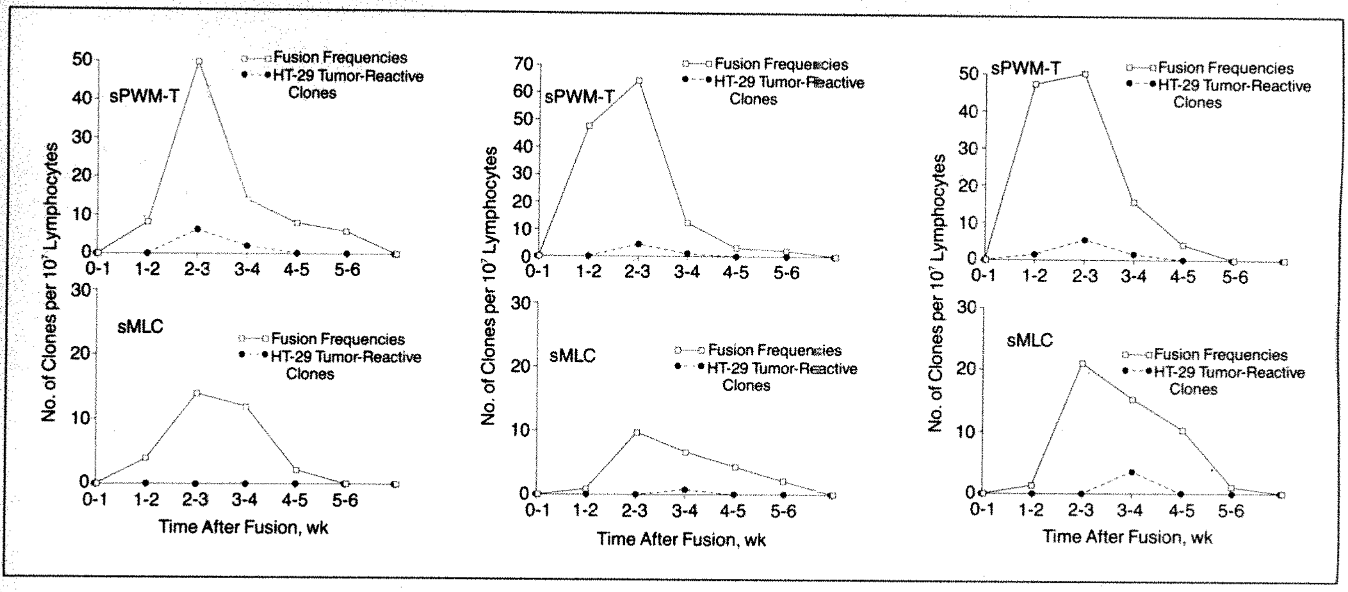


Fig 2.—Comparison of supernatant of pokeweed mitogen–stimulated T lymphocytes (sPWM-T) and supernatant of mixed lymphocytes culture (sMLC) in in vitro immunization. Left, A1 lymph node. Center, A2 lymph node. Right, A3 lymph node.

Table 3.—Effects of CEA Concentration on IVI*

	B1 Lymph Node†		
		IVI with CEA	
	Non-IVI	**20 µg/L**	**40 µg/L**
No. of clones/No. of wells plated (%)	28/288 (9.7)	95/288 (33.0)	48/288 (16.7)
Immunoglobulin isotype, No. of clones			
IgM	22	78	42
IgG	0	5	0
IgA	0	2	3
No. of HT-29 tumor-reactive clones (% of wells plated)	1 (0.3)	5 (1.7)	2 (0.7)
No. of stable HT-29 tumor reactive clones	0	4	1
No. of CEA-reactive clones	0	2	0
Names of stable clones	. . .	CEA 20-1, CEA 20-2, CEA 20-3, CEA 20-4	CEA 40-1

*IVI indicates in vitro immunization; CEA, carcinoembryonic antigen.

†We used lymphocytes from a single lymph node of a patient with colon cancer to generate human monoclonal antibodies by three protocols, two of which used different doses of CEA.

commonly encountered in a majority of colorectal cancers. (2) The serum level of CEA in general is less than 20 µg/L, unless extensive metastases are present. Would a higher dose of CEA have stimulated more efficient IVI? Lymphocytes from a single lymph node (B1) were used for IVI protocols with CEA at both 20 and 40 µg/L (Table 3). The baseline control was fusion between B1 lymphocytes and SHFP-1 cells without CEA. In vitro immunization with CEA at either 20 or 40 µg/L resulted in significantly higher fusion frequencies and greater numbers of HT-29 tumor-reactive hybridomas. In vitro immunization with CEA at 20 µg/L, however, achieved a 200% increase in hybridoma generation and HT-29 tumor-reactive clones compared with the IVI protocol with CEA at 40 µg/L. In addition, IVI with CEA at 20 µg/L was more effective in stimulating IgG secretion, although the IgG clones were not reactive to HT-29 cells. Our results suggested that 20 µg/L was the appropriate dose for IVI protocols using CEA as the immunogen.

Clones secreting HT-29 tumor-reactive HuMAbs at the 96-well stage were expanded. The reactivity of each clone after expansion was retested by ELISA. It was surprising to discover that some human IgMs bound to the ELISA plates in the absence of antigen. This nonspecific binding could not be blocked with either phosphate-buffered saline–bovine serum albumin solution or fetal calf serum. A new standard for determining the positive results of ELISA was established, as described in the "Materials and Methods" section. The supernatants of all expanded clones were further tested by cytoimmunoperoxidase staining of HT-29 cells. The results of ELISA with the new criteria and cytoimmunohistochemical staining demonstrated a close correlation between the two assays (Tables 4 and 5). Sixteen clones were shown to be reactive to HT-29 cells by ELISA. Four of these 16 clones were also reactive to CEA. No false-positive clones were identified by our new criteria for ELISA compared with cytoimmunoperoxidase staining. There was only one false-negative clone according to the new criteria. Therefore, our data suggested that the two criteria for selecting the tumor-reactive clones by ELISA were valid. Figure 3 shows colon cancer cells stained with phosphate-buffered saline–bovine serum albumin solution, negative clone PA2-23, strong positive clones 5K1 and PA1-2, and moderately positive clones PA2-4 and PA1-1. Cells from an additional colon cancer line, CaCO2, were used as target cells in ELISA and cytoimmunoperoxidase staining. The results were in accordance with those using HT-29 cells.

COMMENT

Monoclonal antibodies represent a class of highly specific probes for epitopes on tumor-cell surface antigens. Human monoclonal antibodies are particularly desirable for clinical applications. The theoretical advantages of antitumor

Table 4.—IgM-Secreting Clones With Nonspecific Binding to ELISA Plates*

Names of Clones	Antigen-Coated ELISA Plate†	Optical Density		Cytoimmunoperoxidase Staining of HT-29 Smear
		Antigen-Coated ELISA Plate‡	Non–Antigen-Coated ELISA Plate§	
CEA40-4	HT-29	1.390	1.965	Negative
PA2-23	HT-29	0.740	0.760	Negative
PA2-109	HT-29	0.511	0.497	Negative
MA3-41	HT-29	0.103	0.554	Negative
CK1	HT-29	0.344	0.570	Negative
PA3-21	CEA	0.755	0.605	Negative
CEA20-39	CEA	0.268	0.123	Negative
COL2B-6	CEA	0.333	0.148	Negative

*ELISA indicates enzyme-linked immunosorbent assay; CEA, carcinoembryonic antigen.

†HT-29 was coated onto Falcon type III flexible plates (Becton-Dickinson, Oxnard, Calif); CEA was coated onto either immulon 1 (Dynatech Laboratories Inc, Chantilly, Va) or immunoplate-1 plates (A/S Nunc, Kamstrup, Va).

‡Sample optical density.

§False optical density, nonspecific binding of supernatant to plates without antigen coating.

Table 5.—HT-29 Tumor-Reactive Clones Identified After Expansion

Names of Clones	Lymph Node	Reactivity to HT-29 and CaCO2 by ELISA*	Cytoimmunoperoxidase Staining of HT-29 and CaCO2 Smear†
PA1-1	A1	+	+
PA1-2	A1	+	+ +
PA2-1	A2	+	+
PA2-2	A2	+	+
PA2-3	A2	+	+
MA2-1‡	A2	−	+
PA3-1	A3	+	+
PA3-2	A3	+	+
PA3-3	A3	+	+ to + +
CK2	A3	+	+
CEA20-1	B1	+	+
CEA20-2	B1	+	+ +
CEA20-3	B1	+	+
CEA20-4	B1	+	+
CEA40-1	B1	+	+
SK1	C	+	+ +
SK2	C	+	+

*ELISA indicates enzyme-linked immunosorbent assay. Reactivities were determined by either criterion A or criterion B (see the "Materials and Methods" section). Plus sign indicates a positive reaction; minus sign, a negative reaction.

†Reactivities of antibodies were determined by the presence or absence of a color reaction. Plus sign indicates a moderately intense color reaction; two plus signs, a strong color reaction.

‡A false-negative clone by ELISA screening.

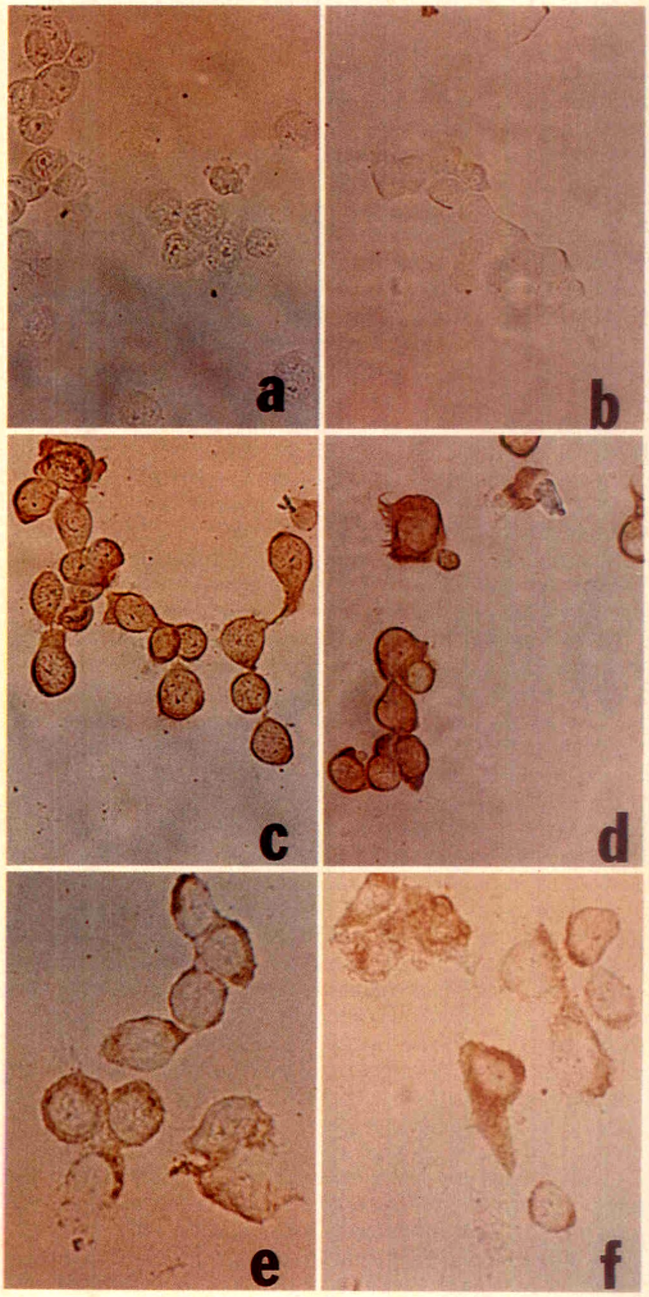


Fig 3.—Cytoimmunoperoxidase staining (original magnification ×400) of HT-29 cells with various human monoclonal antibodies. a and b, Negative control with phosphate-buffered saline–bovine serum albumin solution (a) and negative staining with PA2-23 (b). c and d, Strong positive staining with SK1 (c) and PA1-2 (d). e and f, Moderate staining with PA2-4 (e) and PA1-1 (f).

HuMAbs include the following: (1) Human monoclonal antibodies avoid cross-species sensitization. (2) Human monoclonal antibodies may recognize subtle tumor antigens that can be easily masked by strong, species-specific antigens on the tumor cells in an animal system. (3) The asparagine-linked carbohydrate moiety is more compatible with Fc receptors on human effector cells than with those of mouse antibodies. However, the preparation of HuMAbs specific to tumor-associated antigens has been troubled by a lack of known tumor-specific antigens and by an inability to sensitize human subjects with tumor preparations.

Reports have indicated that cancer patients may have circulating antitumor antibodies.[23-27] Lymphocytes from lymph nodes,[11,16,28-31] peripheral blood lymphocytes,[30] lymphocytes from malignant pleural effusions,[32] and spleen lymphocytes[29,30] of cancer patients have all been used as the source of tumor-specific B lymphocytes. These findings suggest the possibility of an ongoing humoral immune response in cancer patients toward tumor-associated antigens. Our study also supports the idea that lymphocytes from cancer patients may be used as a source of tumor-specific B lymphocytes. However, tumor-specific B lymphocytes are extremely rare. In addition, they may not be in an activated stage that will facilitate cell hybridization. As a result, the yield of clinically interesting HuMAbs is poor in general.

A primary IVI of normal human lymphocytes suggested that an antigen-driven clonal expansion of B lymphocytes facilitates fusion and gives rise to more hybridomas with a defined specificity.[7,33] An antisarcoma HuMAb was produced by such a primary IVI of human splenic lymphocytes with a defined sarcoma antigen.[8]

To effectively generate tumor-specific HuMAbs, a combination of lymphocytes from cancer patients and IVI was studied. Our data suggest that IVI significantly improved fusion frequencies compared with a non-IVI protocol. In addition, the number of tumor-reactive clones was also increased by IVI. This might be related to a selective expansion of antigen-stimulated B lymphocytes. Four CEA-reactive HuMAbs were generated by the IVI protocol with CEA. To our knowledge, this is the first report to describe any CEA-reactive antibodies completely human in origin, although the specificities of these antibodies to CEA have not been determined.

One of the major problems encountered in our IVI study was that, although more IgG- and IgA-secreting hybridomas were produced, an IgG-secreting clone reactive to HT-29 was not obtained. There are several possible explanations. Carcinoembryonic antigen may not be an ideal antigen for stimulating human B lymphocytes against colon cancer. Our study showed that none of the anti-CEA hybridomas were obtained using the non-IVI protocol. It is possible that a primary immune response against CEA is absent in these patients. Thus, an IVI with CEA would fail to stimulate a secondary immune response (ie, antigen-specific IgG). Furthermore, CEA is a soluble antigen that, in general, requires a higher degree of T helper function than a particulate antigen in the production of specific antibodies. T helper lymphocytes in our system might be insufficient to support the CEA-driven immune response. In the future, colon cancer cells instead of CEA will be tested as an immunogen in the IVI protocols. In addition, using a mixture of purified B lymphocytes and a subpopulation of T lymphocytes at various ratios may help to define the proper cellular requirement in IVI. Finally, a crucial cytokine or a combination of various cytokines responsible for isotype switching might be missing or inadequate in our IVI system. Further study to test interleukin 2, interleukin 4, interleukin 6, and gamma interferon in IVI may lead to a better understanding of the cytokines involved in isotype switching of antigen-specific human B lymphocytes.

Regarding the conditions that stimulate B lymphocytes, supernatant of T cells and sMLC were both frequently used in IVI protocols using mouse spleen cells.[34-36] We compared sPWM-T and sMLC in the IVI protocols for producing tumor-reactive HuMAbs. It was found that sPWM-T was superior to sMLC in the following ways: (1) higher fusion frequencies, (2) rapid appearance of hybridomas, (3) more HT-29 tumor-reactive clones, and (4) stable reactive clones. It is likely that the differences resulting from the two protocols were intrinsic properties of the sPWM-T and sMLC preparations, since other experimental conditions were identical and a similar trend was demonstrated by lymphocytes from all three lymph nodes. The other possibility for the inferior quality of sMLC was that the lymphocytes used to prepare sPWM-T and sMLC were completely different. In sMLC, the allogenic lymphocytes were derived from lymph nodes of two different patients. These lymphocytes were not treated with L-leucine methyl ester. In contrast, sPWM-T was derived from peripheral blood lymphocytes of a healthy donor. The T cells were purified by the E-rosette technique. The cytotoxic T lymphocytes and T suppressor cells were removed by L-leucine methyl ester to enrich the T helper lymphocytes. Nevertheless, under the given conditions, sPWM-T appeared to be more suitable than sMLC for IVI.

An unexpected finding in this study was that several human IgMs adhered to ELISA plates nonspecifically. This nonspecific binding was not blockable by bovine serum albumin or fetal calf serum. This cautions us to not depend solely on the conventional interpretation of ELISA results. Two criteria were established to accommodate the high OD reading associated with the binding of some human IgMs to the ELISA plates. Cytoimmunoperoxidase staining of target tumor cells by each supernatant was employed to verify the validity of the new criteria for selecting positive clones by ELISA. The specificity of our new criteria was 100% and the sensitivity was 94%.

To our knowledge, there have been no reports of data obtained by using a combination of lymphocytes from cancer patients and IVI to produce anti-tumor HuMAbs. However, a combination of tumor-infiltrating lymphocytes and in vitro activation by pokeweed mitogen has recently been reported.[37]

Human monoclonal antibodies SKI, PA1-2, and PA3-1 are currently being evaluated for their tumor specificity. The carcinoma-specific antibody will be developed in clinical trials among patients with colon cancer. The epitopes recognized by three HuMAbs will be characterized by biochemical and imunohistochemical methods. Human monoclonal antibodies generated by the method we have described are likely to be clinically useful antibodies. They may also provide a powerful tool to study the biologic characteristics of human cancer.

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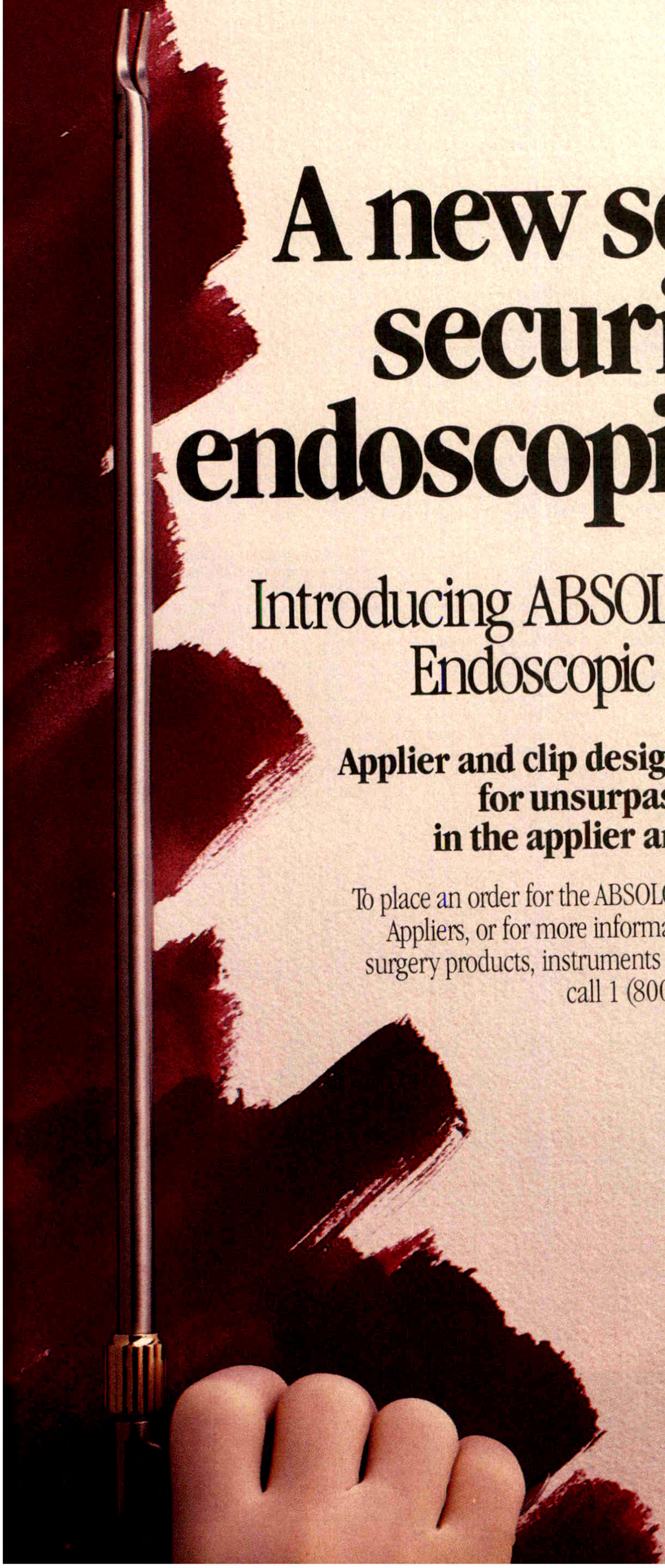

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MAS031

Results of a Multicenter Trial Comparing Imipenem/Cilastatin to Tobramycin/Clindamycin for Intra-abdominal Infections

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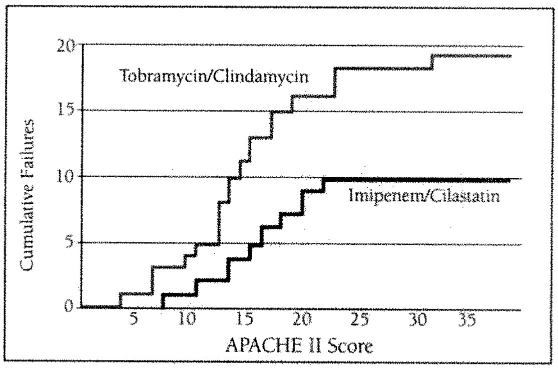
NICOLAS V. CHRISTOU, M.D., Ph.D., RONALD W. BUSUTTIL, M.D., Ph.D.

"We designed a multicenter study to compare tobramycin/clindamycin to imipenem/cilastatin for intra-abdominal infections. We included the Acute Physiology and Chronic Health Evaluation (APACHE II) index of severity and excluded patients without established infection. Two hundred ninety patients were enrolled, of whom 162 were evaluable [81 patients in each treatment group]. Using logistic regression to analyze both outcome at the abdominal site of infection and outcome as mortality, we found a significant correlation for both with APACHE II score ($p<0.0001$ for both). Next we analyzed the residual effect of treatment assignment and found a significant improvement in outcome for imipenem/cilastatin-treated patients ($p=0.043$)."

"The differences in outcome were explained by a higher failure rate for patients with gram-negative organisms for tobramycin/clindamycin-treated patients ($p=0.018$)."

FAILURE AS A FUNCTION OF APACHE II SCORE AND ANTIBIOTIC REGIMEN — PATIENTS WITH GRAM-NEGATIVE INFECTIONS



Results for evaluable patients harboring gram-negative organisms. APACHE II score ($X^2=8.95$, $p=0.0028$) and treatment ($X^2=5.65$, $p=0.0175$) were both significant predictors of failure for this patient group.

"This study supports inclusion of severity scoring in statistical analyses of outcome results.... Imipenem/cilastatin was found to be significantly more effective against facultative gram-negative organisms than tobramycin...." (Ann. Surg. *212*:581-591, 1990.)

PRIMAXIN®

(Imipenem-Cilastatin Sodium|MSD)

DEFINING A NEW STANDARD† FOR EMPIRIC THERAPY

† when indicated organisms are suspected at indicated sites

PRIMAXIN is indicated for the treatment of intraabdominal infections caused by organisms designated in the Prescribing Information.

PRIMAXIN is contraindicated in patients who have shown hypersensitivity to any component of this product. Before initiating therapy with PRIMAXIN, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams, and other allergens.

If an allergic reaction to PRIMAXIN occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine and other emergency measures.

For a Brief Summary of Prescribing Information, please see the following page.

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PRIMAXIN®

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DEFINING A NEW STANDARD† FOR EMPIRIC THERAPY

† when indicated organisms are suspected at indicated sites

Contraindications: PRIMAXIN® (Imipenem-Cilastatin Sodium, MSD) is contraindicated in patients who have shown hypersensitivity to any component of this product.

Warnings: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA LACTAM. BEFORE INITIATING THERAPY WITH 'PRIMAXIN,' CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO 'PRIMAXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte, and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General* – CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

Patients with creatinine clearances of ≤5 mL/min/1.73 m^2 should not receive PRIMAXIN unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions – Generalized seizures have been reported in patients who received ganciclovir and PRIMAXIN. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility – Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN), and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Pregnancy – Pregnancy Category C: Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN® (Imipenem-Cilastatin Sodium, MSD) at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea, and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in nonpregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are under way to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use – Safety and effectiveness in infants and children below 12 years of age have not yet been established.

Adverse Reactions: PRIMAXIN is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions – Local adverse clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), infused vein infection (0.1%).

Systemic Adverse Reactions – The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were: nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal* – pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, hepatitis (rarely), gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS* – encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses* – transient hearing loss in patients with impaired hearing, tinnitus, taste perversion; *Respiratory* – chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular* – palpitations, tachycardia; *Skin* – toxic epidermal necrolysis (rarely), erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a Whole* – polyarthralgia, asthenia/weakness; *Renal* – acute renal failure (rarely), oliguria/anuria, polyuria. The role of PRIMAXIN in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

Adverse Laboratory Changes – Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic* – increased SGPT, SGOT, alkaline phosphatase, bilirubin, and LDH; *Hemic* – increased eosinophils, positive Coombs test, decreased WBC and neutrophils, including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes* – decreased serum sodium, increased potassium, increased chloride; *Renal* – increased BUN, creatinine; *Urinalysis* – presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

NOTE: Due to the high antimicrobial activity of PRIMAXIN, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

How Supplied: PRIMAXIN is supplied as a sterile powder mixture in vials, infusion bottles, and single-dose ADD-Vantage®† vials containing imipenem anhydrous and cilastatin sodium as follows: 250 mg imipenem equivalent and 250 mg cilastatin equivalent; 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

Caution: The suspension from vials is not for direct infusion.

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Detection of Primary Colorectal Cancer With Indium 111 Monoclonal Antibody B72.3

Ralph J. Doerr, MD; Hani Abdel-Nabi, MD, PhD; Jon M. Baker, MD; Steven Steinberg, MD

• B72.3 is a murine monoclonal antibody of the immunoglobulin subclass IgG1 directed against TAG-72, a cell surface antigen present on colorectal carcinoma cells. We investigated the utility of scanning with indium 111–labeled B72.3 in 16 patients with a high clinical suspicion of or biopsy-proven primary colorectal cancer. Each patient received 1 or 2 mg of B72.3 monoclonal antibody labeled with 152 MBq of indium 111. Patients underwent scanning 2 to 3 days and 7 days after infusion by planar and emission computed tomography. Nineteen lesions were confirmed in 12 patients. Three patients with benign polyps had true-negative monoclonal antibody scans. Indium 111–labeled imaging of B72.3 detected nine of 19 lesions. Unsuspected tumor sites were identified by monoclonal antibody scan in three patients. By detection of additional abdominal disease and extra-abdominal spread, indium 111–labeled scanning of B72.3 directly affected treatment in 18% of patients.

(*Arch Surg.* 1990;125:1601-1605)

Primary colorectal carcinoma is usually diagnosed with a combination of physical examination, barium enema, sigmoidoscopy, or colonoscopy with biopsy. Accurately determining the extent of tumor both locoregionally and at distant sites forms the basis for staging and influences the therapeutic approach. Despite new advances in cross-sectional imaging with ultrasound, computed tomographic (CT) scan, and magnetic resonance imaging, staging is incomplete and ordinarily awaits histopathologic examination of the specimen. Recently, the strategy for presurgical detection and staging has been expanded by the use of monoclonal antibodies (MoAbs) labeled with radioisotopes directed against tumor-associated antigens.[1-7] Excellent tumor localization has been achieved with minimal reported toxicity.[8]

Monoclonal antibody B72.3 targets the tumor-associated glycoprotein TAG-72 found on the cell surface of up to 94% of colon adenocarcinomas.[9] In previous studies, B72.3 labeled with iodine 131 demonstrated 75% of tumor lesions with excellent ratios of tumor to normal tissue.[10] A variety of tumor sites including primary, recurrent, and metastatic colorectal lesions have been identified by radioisotope concentration, including occult tumors missed by conventional diagnostic tests.[5]

In this study, we present the effectiveness of indium 111–labeled B72.3 immunoscintigraphy in localizing primary colorectal cancers and the locoregional and distant spread at the time of presentation.

MATERIALS AND METHODS

A total of 16 patients were studied under this prospective, multi-institutional, open-labeled, nonrandomized trial. All patients were men whose ages ranged from 60 to 79 years, with a mean ± SD of 67.9 ± 5.4 years. Thirteen patients were suspected of having primary colorectal cancer. All 13 patients had colonoscopy- or biopsy-proven adenocarcinoma of the colon and/or rectum. Three patients had multiple polyps. The preinfusion workup in all the patients included the following: (1) physical examination, (2) history pertinent to previous MoAb injection and concomitant medications, (3) blood workup including complete blood cell count with differential, platelets, liver functions, kidney functions, and tests. Patients also had serum TAG-72 level evaluations. Prior to the antibody infusions, a baseline serum sample was obtained for the evaluation and the study of the development of human antimouse antibodies. Diagnostic workup included a colonoscopy on all patients, barium enema (double contrast in all patients), CT scan of the abdomen and pelvis, chest roentgenograms, and baseline electrocardiogram.

After giving informed consent according to the local institutional review board requirements, each patient received either 1 or 2 mg of B72.3 labeled with 162.8 to 185 MBq of ^{111}In. The B72.3 ^{111}In labeled by the carbohydrate linker specific technique of glycyl-tyrosyl-diethylenetriaminepentaacetic acid is referred to as CYT-103. Planar and single photon emission CT imaging was performed 3 days and 5 to 7 days following the infusion. All patients went to surgery within 3 to 16 days after the second scanning session. The results of the scans were communicated to the surgeon prior to the scheduled surgery.

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Findings in Patients With CYT-103 Immunoscintigraphy*

Patient No./ Age, y	Disease Site at Presentation	Histologic Findings†	Tumor Cells Expressing TAG-72, %	Additional Lesions Found on MoAb
1/68	Sigmoid colon‡	Adenocarcinoma	50	Right iliac bone
	Rectum‡	Adenocarcinoma	50	. . .
2/60	Ascending colon	MWD adenocarcinoma, metastatic lymph node (2/3)	. . .	. . .
3/59	Ascending colon, transverse colon	Polyps: necrosis and marked dysplasia	. . .	. . .
4/60	Suspected hepatic flexure	Not done	. . .	Left 6th rib
	Right lobe of liver	MWD adenocarcinoma	. . .	7th, 8th thoracic vertebrae, iliac bone bilaterally
5/66	Rectum	WD adenocarcinoma	. . .	. . .
6/66	Ascending colon‡	MWD	15	Left supraclavicular lymph node
	Liver	Metastatic adenocarcinoma with necrosis, metastatic lymph node (11/25)	. . .	. . .
7/69	Colonic polyps	Multiple polyposis	. . .	. . .
8/67	Hepatic flexure‡	MWD	90	. . .
9/75	Ascending colon polyp	Adenocarcinoma in situ	. . .	. . .
10/72	Ascending colon‡	Adenocarcinoma	60	. . .
11/79	Sigmoid	MWD adenocarcinoma	. . .	. . .
12/69	Hepatic flexure‡	MWD adenocarcinoma	60	. . .
	Liver	Metastatic adenocarcinoma, metastatic lymph node (2/2)	30	. . .
13/64	Rectum	Focus adenocarcinoma in villous adenocarcinoma	ND	. . .
14/68	Cecum	WD adenocarcinoma in a villous adenoma	. . .	. . .
15/62	Rectum‡	MWD adenocarcinoma arising from villous adenoma	10	. . .
16/64	Ascending colon	Tubular adenomas (5)	. . .	. . .

*MWD indicates moderately well differentiated; WD, well differentiated; TAG-72, a cell surface antigen present on colorectal carcinoma; MoAb, monoclonal antibody; and ND, not done.

†Numbers in parentheses indicate number of lymph nodes.

‡Positive findings on MoAb scan. Patient 4 had a negative cold defect finding on MoAb scan.

RESULTS

Nineteen separate adenocarcinoma lesions were identified in 12 patients (Table) at the following locations: bowel, 12 (five in the rectosigmoid, one in the transverse colon, and six in the cecum and ascending colon); lymph node, four (three in the mesenteric and one in the neck); and liver, three. Three patients with a preoperative diagnosis of polyps were confirmed at surgery to have benign polyps. One patient had complete excision of adenocarcinoma in situ in a rectal villous adenoma. In these four patients, the ^{111}In scans had negative results and were considered to be true negative findings. In the remaining 12 patients, seven had only one lesion, while five had several lesions either in the regional site of the tumor or distant metastases to the liver, lymph nodes, or bone.

Results of CYT-103 imaging were true-positive in seven of 12 bowel lesions and two of four lymph node metastatic lesions. Liver lesions were missed in two patients and appeared as cold defect in a third patient. In three patients, previously unsuspected additional lesions were identified with the MoAb scan and were confirmed. These lesions were in the right iliac bone in one patient (patient 1), consistent with bone metastasis confirmed by a bone scan. In another patient (patient 4), there was a lesion in the left sixth rib and in the seventh and eighth thoracic vertebrae (Figs 1 and 2), as well as the sacroiliac joints, highly suggestive of metastatic disease to the bone. By open biopsy, the left sixth rib lesion was proved to be metastatic adenocarcinoma. In the third patient (patient 6), the antibody scan identified a left supraclavicular lymph node (Fig 3, left) that was resected and confirmed to be a metastatic adenocarcinoma from a bowel primary site (Fig 3, right). Incidentally, this patient also presented with a right colon lesion and was worked up with the possibility of another primary tumor in the head and neck region. The patient was subsequently treated with a radical neck dissection that tested negative for a primary tumor. All lymph nodes were adenocarcinoma, consistent with a finding of primary tumor in the bowel.

The sensitivity of the MoAb scan in this cohort of patients is slightly lower than expected, identifying only nine of 19 lesions. However, one of these lesions was carcinoma in situ and well beyond the resolution of existing gamma camera capabilities. If we exclude this patient, then the MoAb scan successfully identified nine of 18 lesions. Seven of 11 bowel primary sites were imaged and confirmed, for a sensitivity of 63%. In the remaining bowel lesions that tested negative for tumor, there was no expression of the antigen TAG-72. Thus, from an immunoaffinity point of view, ^{111}In-labeled CYT-103 identified all primary lesions that expressed TAG-72, for a sensitivity of 100%. The expression of TAG-72 in the lesions varied

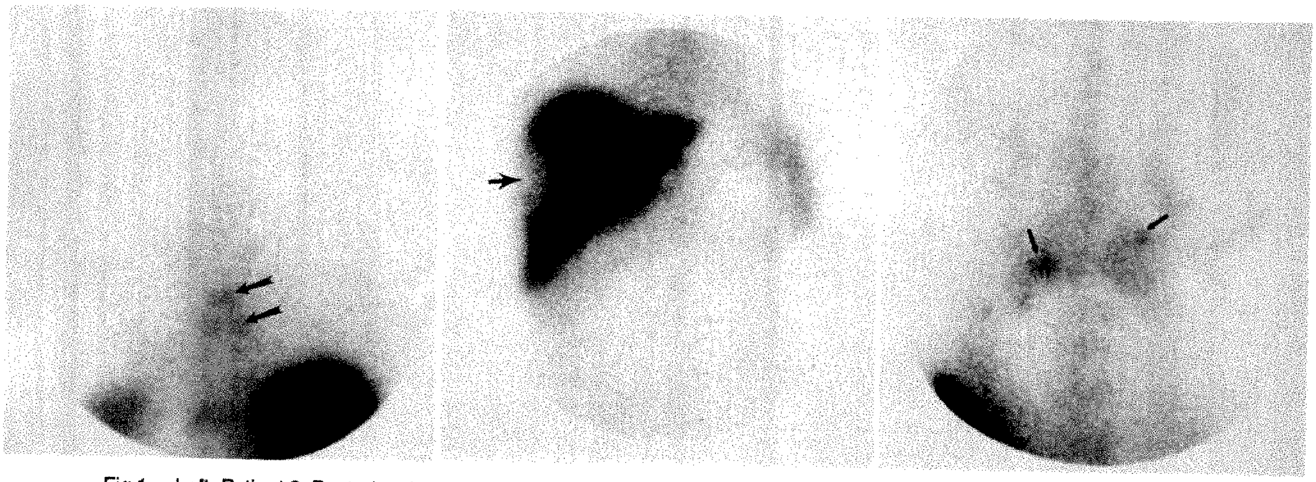

Fig 1.—Left, Patient 6. Posterior view of the chest following CYT-103 administration, showing two previously unsuspected lesions at the level of the seventh and eighth thoracic vertebrae (arrows). Center, Same patient with a large liver mass (arrows). Right, Bony metastases were also demonstrated (arrows) in the pelvis posteriorly.

from 15% to 90%. Those lesions that were TAG-negative or had TAG in less than 5% of the cancer cells were not imaged with the CYT-103, thus confirming our previous observation.[11] Serum TAG-72 levels, elevated in only four patients, had no influence on immunoscintigraphy.

Human antimouse antibody formation was identified in three patients (18%). No adverse reactions or clinically significant changes in bone marrow, liver, or kidney functions were detected in patients receiving ^{111}In B72.3.

COMMENT

Colorectal cancer remains the most common visceral malignancy in the United States.[12] Despite newer diagnostic adjuncts, 50% of patients harbor undetected micrometastases at the time of their presentation and will die of their disease.[13] More accurate staging at presentation would permit tailoring of adjunctive therapy to individual patients. This would require detection of tumor deposits in lymph nodes and other soft tissues in the abdomen and retroperitoneal area and distant sites commonly missed by other diagnostic modalities. The identification of occult disease could help define the surgical procedure to be undertaken or dictate further directed diagnostic workup.

Locoregional recurrence of colorectal carcinoma is related to the depth of the tumor bowel wall penetration (Dukes' B), presence of lymph node metastases (Dukes' C), and invasion of adjacent organs (Dukes' B_3-C_3).[14] Advancing Dukes' classification predicts local recurrence as well as declining 5-year survival.[15] Involvement of regional lymph nodes, while the most common form of colorectal cancer spread, remains difficult to detect preoperatively. Ultrasound study and CT scan are of limited value in detecting pathologic lymph nodes. If 1.5 cm represents the upper limit of normal lymph node size, CT scan reliably identifies lymph node metastases in only one third of the cases. The preponderance of nodal metastases are found in normal-sized lymph nodes.[16] Recent reports of improved 5-year survival with wider, more extensive lymphadectomy at the time of resection of a primary colorectal cancer makes the question of detecting lymph node metastases preoperatively more important.[17]

Recent observations of survival benefit accruing from en bloc resection of adherent or tumor-infiltrated adjacent viscera or abdominal wall at the time of the primary colorectal resection direct attention to a more accurate preoperative staging of local tumor extent.[18]

Metastatic spread to the liver will be found in approximately 20% of patients at the time of diagnosis of primary colorectal carcinoma.[19] Among the available cross-sectional imaging agents, CT scan remains superior, with a sensitivity of 73% and specificity of 99%.[20] Magnetic resonance imaging has been useful in evaluating anatomic disposition of metastases relative to hilar vessels and hepatic veins, crucial to planning operative removal. Again, smaller liver metastases are missed with CT scan, even with contrast-enhanced hepatic artery injection.

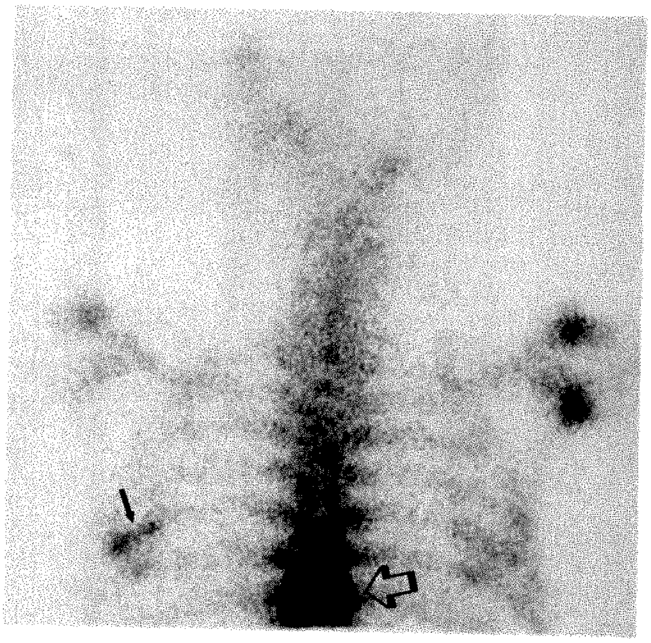

Fig 2.—Patient 6. Scan showing posterior projection. In addition to the thoracic spine lesions (open arrow), involvement of the left sixth rib is also demonstrated (closed arrow).

The discovery of carcinoembryonic antigen led to a new concept in immunodiagnosis.[21] Several radiolabeled polyclonal antibodies, and, more recently, MoAbs, were raised to these tumor-associated antigens. Subsequent work demonstrated that radiolabeled MoAbs could be safely injected and could detect tumors with a reasonable sensitivity and specificity.[1-7,22]

In this study, we successfully detected 63% of primary colorectal carcinomas. As we have noted before, there is a

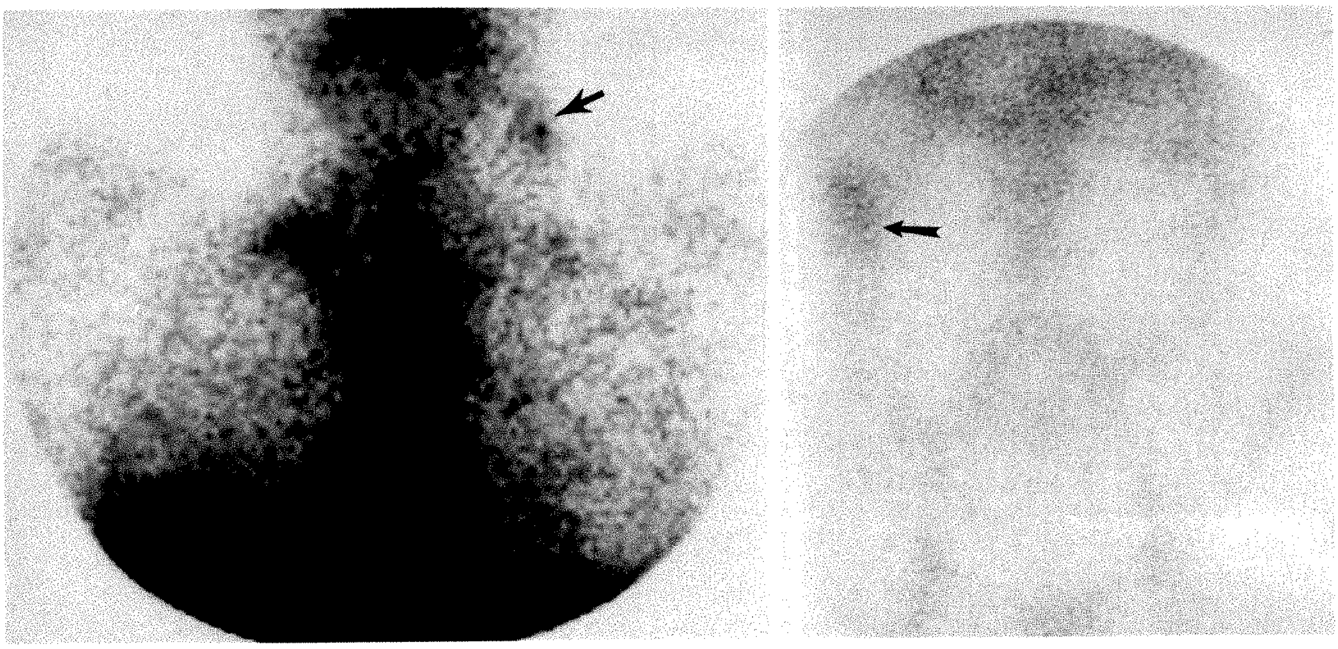

Fig 3.—Left, Abnormal CYT-103 accumulation identified in the left supraclavicular region (arrow). Right, Primary adenocarcinoma of the ascending colon (arrow) in the same patient.

correlation between the presence of TAG-72 in resected specimens and ^{111}In–labeled B72.3 detectability of these lesions.[11] In contrast, there is no correlation between serum TAG-72 levels and successive tumor imaging with CYT-103. Difficulty in interpretation arises because of nonspecific radioaccumulation in the bowel. If the two cases with predominant bowel activity are excluded, the sensitivity of CYT-103 for primary colon lesion is 100%. The high specificity of CYT-103 is demonstrated in the three patients who presented with equivocal biopsies of polypoid colonic lesions. While suspicious for adenocarcinoma preoperatively, the MoAb scans showing negative results were confirmed by the finding of benign polyps on resected specimens. The addition of single photon emission CT imaging provided better anatomic definition of the primary tumors and resulted in improvement in tumor detection in four patients.

The low rate of human antimouse antibody formation and absence of adverse reactions observed in this study are in accordance with results of recent studies with this MoAb.[22] In the four patients with mesenteric lymph node involvement, ^{111}In–labeled MoAb imaging failed to detect these lesions. Positive lymph nodes less than 1 cm in diameter in the mesentery or retroperitoneum are below the detection capability of the gamma camera, even with the use of single photon emission CT. If the lymph nodes are close to a primary tumor with a high uptake of radiolabeled antibodies, they are not distinguishable from the primary lesion.[23]

As has been previously observed, hepatic metastases can appear on MoAb scan as filling defects, positive accumulations, or both.[24] The degree of differentiation of these synchronous liver lesions, irrespective of mucin production or the presence of necrosis, also affects imaging accuracy.[22]

The most important aspect of immunoscintigraphy is the ultimate impact on treatment of patients. Beatty et al[25] reported that the major advantage of MoAb scanning is in the detection of extra-abdominal metastases. In reviewing a large European patient experience, Baum et al[26] found immunoscintigraphy to be helpful, primarily complementing other diagnostic methods, in 46% of patients. In 20% of their cases, the MoAb scan contributed unique formation, eg, identifying abdominal or lymph node metastases and pelvic recurrences missed by conventional workup. Finally, immunoscintigraphy was felt to be decisive for a change in treatment strategy, eg, institution of radiotherapy or second laparotomy in 13%.

In a large multicentered trial, CYT-103 radiolabeled with ^{111}In correctly identified colorectal adenocarcinoma lesions at a 70% sensitivity and a 90% specificity. The investigators considered immunoscintigraphy to be beneficial or very beneficial in 26% of patients. The benefit accrued from detecting previously occult synchronous lesions, identifying localized disease without regional or metastatic spread, and confirming adenocarcinoma when other diagnostic test results were equivocal.[27]

In this study, the sensitivity of the MoAb scan is slightly lower than expected, identifying only nine of the 19 confirmed lesions. If the in situ carcinoma is excluded, and one only looks at lesions that express TAG-72 in the resected specimen, then CYT-103 identified all primary tumors. The variability of TAG-72 expression in the tumor dictates the success of immunoscintigraphy with CYT-103.

We found MoAb scan results to directly affect the diagnostic and treatment strategy in 18% of our patients. In keeping with the observations of Beatty et al[25] in these patients with primary colorectal cancer, the MoAb scan was seen to affect their treatment with the detection of additional abdominal disease (hepatic metastasis) and extra-abdominal spread (bone and distant lymph node metastases). The addition of targeted cross-sectional imaging and needle biopsies of MoAb-detected lesions followed by the institution of systemic therapy and radiotherapy defines the advantage of immunoscintigraphy in this study.

The high specificity and documented safety combine to make ^{111}In–labeled B72.3 a promising clinical tool in the evaluation and staging of primary colorectal cancer.

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In Other AMA Journals

ARCHIVES OF DERMATOLOGY

Neurologic Disease in Human Immunodeficiency Virus–Infected Drug Abusers

Renee Malouf, MD; Germaine Jacquette, MD; Jay Dobkin, MD; John C. M. Brust, MD

Previous studies of human immunodeficiency virus–related neurologic disease have been either retrospective or have included mostly homosexual patients. We sought to determine (1) the true prevalence of neurologic abnormalities in patients with acquired immunodeficiency syndrome or lymphadenopathy acquired immunodeficiency–related complex, and (2) whether differences in prevalence or type of neurological abnormality exist between parenteral drug abusers and non–parenteral drug abusers. We prospectively evaluated 190 adult inpatients with either acquired immunodeficiency syndrome (129) or lymphadenopathy acquired immunodeficiency–related complex (61); 151 (80%) were parenteral drug abusers, and 172 patients (91%) had neurologic symptoms or signs. There was no significant difference in prevalence of neurologic disease between parenteral drug abusers and non–parenteral drug abusers, or between patients with acquired immunodeficiency syndrome and those with lymphadenopathy acquired immunodeficiency–related complex. The prevalence of neurologic symptoms in these patients with lymphadenopathy acquired immunodeficiency–related complex and acquired immunodeficiency syndrome is the highest reported to date and appears to reflect the prospective nature of the study (*Arch Neurol.* 1990;47:1002-1007).

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Calcium and Calcium Binding in Human Gallstone Disease

Lillian G. Dawes, MD, Robert V. Rege, MD

• Precipitation of calcium salts from bile is important in pigment gallstone formation and may serve as a nidus for cholesterol precipitation. We compared gallbladder bile from patients with symptomatic gallstone disease (40 with cholesterol gallstones and 12 with pigment gallstones) with bile from 10 patients undergoing surgery for non–biliary tract disease. Bile from patients with gallstone disease was less concentrated, with decreased sodium, bile salt, and phospholipid concentrations, but elevated biliary calcium concentrations were not observed. The relationship between free ionized calcium and total calcium was similar in all groups, indicating no difference in calcium binding by gallstone-containing bile. We cannot exclude elevated biliary calcium level as a factor in gallstone pathogenesis, as it could be a transient event. The importance of calcium precipitation was supported by our finding that more than half of the samples were saturated or supersaturated with at least one calcium salt, calcium carbonate.

(*Arch Surg.* 1990;125:1606-1609)

Supersaturation of bile with cholesterol is a known prerequisite for the formation of cholesterol gallstones, the most common type of gallstone in the United States.[1,2] Yet, bile is normally supersaturated with cholesterol during the interdigestive period and gallstones do not develop in everyone with bile supersaturated with cholesterol.[3] Other factors—nucleating or antinucleating agents—have been shown to influence cholesterol precipitation and to help to determine if and when it will occur.[3-5] Calcium salts are found in the center of most, if not all, cholesterol gallstones,[6] leading to the hypothesis that calcium salt precipitates may act as a "nidus" for cholesterol gallstone formation and precipitate on the surface of these stones, interfering with dissolution therapy and gallstone lithotripsy. Moreover, 10% to 27% of patients have pigment gallstones composed largely of calcium salts of bilirubinate, carbonate, phosphate, or palmitate.[2] Calcium salts, therefore, play an important role in the pathogenesis of all types of gallstones.[7]

To determine whether elevations in biliary calcium level occur routinely in patients with gallstones, we compared bile from patients with cholesterol and pigment gallstones, retrieved at the time of cholecystectomy, with bile from patients without hepatobiliary disease. A reduction in the degree of gallbladder bile concentration but no elevations in biliary calcium concentrations were found in patients with gallstones at the time of operative treatment for symptomatic gallstones.

PATIENTS AND METHODS

Gallbladder bile was collected from 62 patients at laparotomy through a protocol approved by the Institutional Review Board of Northwestern University, Chicago, Ill, and informed consent was obtained in each case. All patients fasted for a similar period beginning the night before surgery. Patients with acute cholecystitis, cystic duct obstruction, abnormal results of liver function tests, or bacterial infection and those receiving parenteral nutrition were excluded. Fifty-two patients had symptomatic chronic cholelithiasis, while 10 control patients were undergoing elective upper abdominal operations for diseases unrelated to biliary tract disease. Bile was aspirated from the fundus of the gallbladder into a syringe with a 20-gauge needle. In control patients, the needle puncture site was closed with a 6-0 Prolene suture to ensure that no bile leakage occurred. Air was removed from the syringe, and the syringe was capped, protected from light, placed on ice, and transported to the laboratory anaerobically for immediate analysis of pH, P_{CO_2}, total calcium, free ionized calcium (Ca^{++}), sodium, and potassium levels, as previously reported.[8] Bicarbonate and carbonate concentrations were calculated with use of the Henderson-Hasselbalch equation, and calcium carbonate saturation indexes (SIs) were determined with use of a solubility product ($Ksp = 3.78 \times 10^{-8}$), as previously described.[8-10]

Aliquots of bile were diluted with isopropanol and frozen for later determination of cholesterol and phospholipid concentrations by end-point enzymatic methods with use of a phospholipid kit (Wako Corporation, Osaka, Japan) and a cholesterol assay kit (Boehring-Mannheim Biochemical, Mannheim, Federal Republic of Germany). Similarly, aliquots of bile were diluted with methanol and frozen for later determination of total bile salt (BS) concentrations by the 3-α-hydroxysteroid dehydrogenase method.[10] Cholesterol SIs were determined by the method of Thomas and Hofmann.[11] Gallstones were classified by visual inspection and/or infrared spectra analysis.[12]

Statistical analysis was performed with analysis of variance to compare differences between groups. Multiple regression analysis was used to assess relationships between variables. $P < .05$ was considered significant.

RESULTS

No complications, such as bile leaks or postoperative subhepatic infections, occurred as a result of bile sampling. Gallbladders in control patients appeared normal on visual inspection and contained no gallstones by palpation. Twenty-five (approximately 50%) of patients with gallstones underwent infrared analysis of their gallstones. Gallstones were classified as cholesterol gallstones if they contained greater than 25% cholesterol by weight or pigment gallstones if they contained large amounts of bilirubinate and less than 25% cholesterol. In every case, infrared and visual classification were in agreement. Of the 52 patients, 40 had cholesterol gallstones and 12 had pigment gallstones.

Biliary Acidification

An inverse linear relationship is observed in normal bile between bile pH and BS concentrations. A similar relation-

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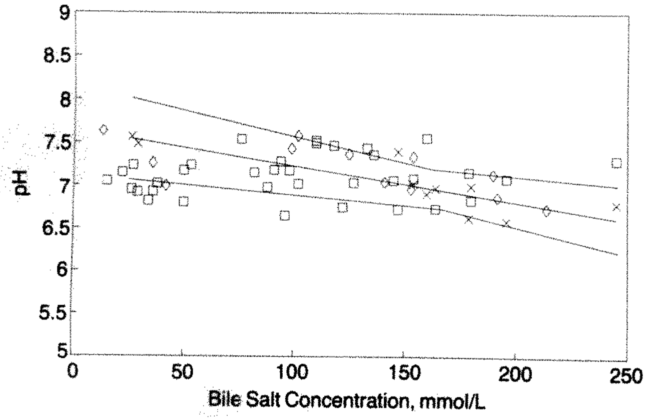

Fig 1.—Linear relationship of pH (7.65 − 0.0042 × bile salt concentration [r = .84]) and bile salt concentration. The regression line and 95% confidence intervals for normal bile are shown. This relationship is not altered in bile from patients with gallstones. Squares indicate patients with cholesterol gallstones; diamonds, patients with pigment gallstones; and *X*'s, control patients.

ship is seen with bile from patients with gallstones, suggesting normal bile acidification during concentration by the gallbladder. Although pH in samples from patients with gallstones varied from control values, most of the values fell within the 95% confidence interval (Fig 1), and mean pH was slightly, although not significantly, lower in control patients when compared with values in patients with cholesterol gallstones or pigment gallstones (Table). Mean biliary Pco$_2$ was higher than that in normal serum but was similar between groups. The calcium carbonate SIs calculated from biliary free Ca^{++} and carbonate concentrations are shown in Fig 2. Although mean (±SD) SIs in control patients (2.54 ± 1.0), patients with cholesterol gallstones (1.8 ± 0.3), and patients with pigment gallstones (3.61 ± 1.0) were not statistically different, the majority of samples, irrespective of group, were saturated or supersaturated (SI$\geq$1.0) with calcium carbonate.

Biliary Electrolytes and Lipids

Mean biliary sodium and potassium concentrations were significantly lower, while mean chloride concentration was slightly, although not significantly, higher in patients with gallstones compared with control patients (Table). These results are consistent with a lower degree of bile concentration in gallbladders that contain symptomatic gallstones, irregardless of stone type. In agreement, mean BS concentration was decreased significantly in patients with cholesterol gallstones (148 ± 22 mmol/L) and slightly in patients with pigment gallstones (122 ± 19 mmol/L) compared with control patients (94 ± 8 mmol/L). Mean phospholipid concentration was lower in bile from patients with cholesterol and pigment gallstones (33 ± 3 mmol/L and 30 ± 6 mmol/L, respectively) than in bile from control patients (61 ± 4 mmol/L).

Mean cholesterol concentration was highest in control patients (15.5 ± 1.6 mmol/L) but was not statistically different in patients with cholesterol (13.0 ± 1.4 mmol/L) or pigment (11.6 ± 2.8 mmol/L) gallstones. However, because of decreased BS and phospholipid concentrations, the molar percent of cholesterol in cholesterol gallstone–containing bile (9.7% ± 0.7%) was significantly higher than that in control patients (6.1% ± 0.6%) and patients with pigment gallstones (7.2% ± 1.0%) and resulted in a 1.8-fold elevation of the cholesterol SI in cholesterol-forming biles (patients with cholesterol stones, 1.12 ± 0.2; patients with pigment stones, 0.76 ± 0.1; and control patients, 0.61 ± 0.1).

Gallbladder Bile Electrolyte Composition

	Control	**Cholesterol Gallstones**	**Pigment Gallstones**
pH	6.88 ± 0.33	7.03 ± 0.28	7.05 ± 0.28
Pco$_2$, mm Hg	57 ± 2	50 ± 2	54 ± 4
Sodium, mmol/L	221 ± 5	180 ± 4*	181 ± 10*
Potassium, mmol/L	14.2 ± 1.1	9.1 ± 0.6*	9.9 ± 1.4*
Chloride, mmol/L	57 ± 13	75 ± 6	70 ± 11
Free ionized calcium, mmol/L	1.65 ± 0.1	1.4 ± 0.1	1.71 ± 0.2
Total calcium, mmol/L	7.98 ± 1.1	5.7 ± 0.4*	6.42 ± 0.8

*Significant difference at $P<.05$.

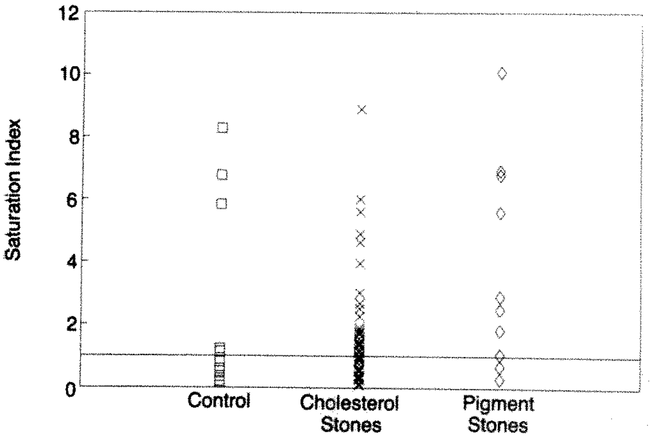

Fig 2.—Saturation indexes for calcium carbonate. Although the average saturation index for calcium carbonate is similar for bile from control patients and bile from patients with cholesterol and pigment gallstones, more than half of all patients have bile that is saturated or supersaturated (saturation index $\geq$1) with calcium carbonate. Squares indicate control patients; *X*'s, patients with cholesterol gallstones; and diamonds, patients with pigment stones.

Biliary Calcium

Free Ca^{++} concentration in bile from control patients was directly related to total calcium concentration by a linear relationship: Free Ca^{++} = 0.13 × total calcium concentration + 0.66 (r = .77) (Fig 3). All but a few calcium values from patients with gallstones fell within the 95% confidence limits of the regression line seen in Fig 3, suggesting that the relationship between free Ca^{++} and total calcium concentrations was not altered in patients with gallstones. By inference, binding or "buffering" of calcium in all bile samples was similar.

As previously reported,[8,13] free Ca^{++} and total calcium concentrations were linearly related to the BS concentration in bile from patients without gallstones by the following relationships: Free Ca^{++} = 1.15 + 0.0034 × BS concentration (r = .56) (Fig 4, top) and total calcium = 2.58 + 0.037 × BS concentration (r = .70) (Fig 4, bottom). Note that the intercepts at extrapolations to BS concentration = 0 are the approximate values of human serum free Ca^{++} and total calcium. Except for three patients with pigment gallstones and two patients with cholesterol gallstones whose free Ca^{++} levels were higher than the 95% confidence interval, free Ca^{++} was not elevated in patients with cholesterol or pigment gallstones. A lack of elevation in biliary calcium is also exemplified by a comparison of mean calcium values between groups. As expected with a lower degree of concentration of bile in patients with gallstones, free Ca^{++} and total calcium concentrations were lower

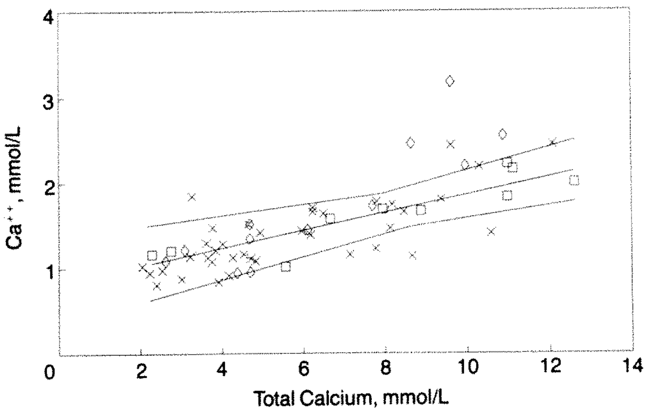

Fig 3.—Relationships of biliary free ionized calcium (Ca^{++}) concentration (0.103 × total calcium level + 0.82 [*r* = .89]) to total calcium concentration. As in other species, Ca^{++} concentration is linearly related to the total calcium concentration. The linear regression analysis and 95% confidence intervals for normal bile are shown. Note that the majority of samples from patients with gallstones fall within these intervals. Squares indicate control patients; *X*'s, patients with cholesterol stones; and diamonds, patients with pigment stones.

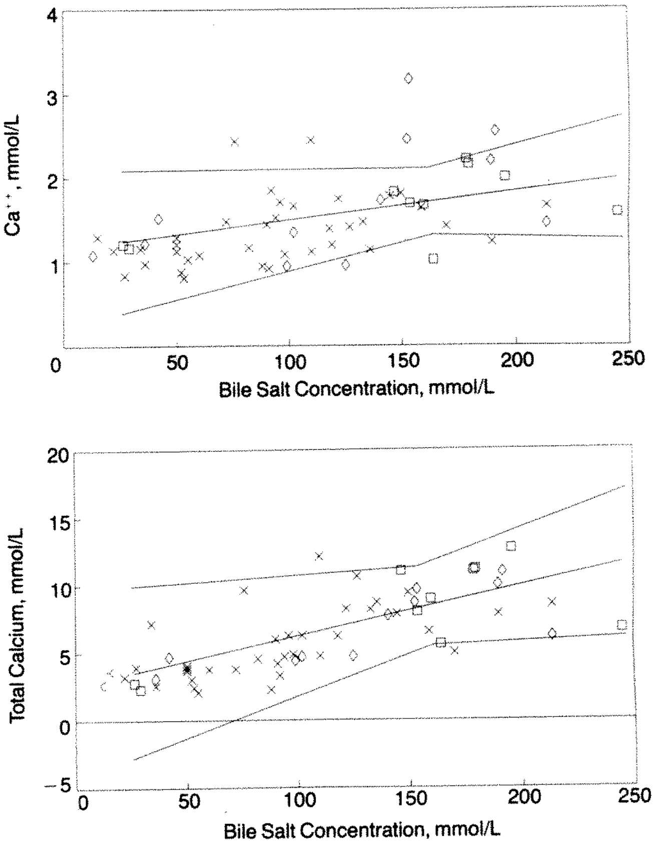

Fig 4.—Free ionized calcium (Ca^{++}) (1.15 + 0.0034 × bile salt concentration [*r* = .56]) and total calcium (2.58 + 0.037 × bile salt concentration [*r* = .70]) concentrations as a function of bile salt concentration. The linear relationship and 95% confidence intervals of both Ca^{++} (top) and total calcium (bottom) concentrations to the biliary bile salt concentration demonstrates that this relationship is not altered in bile from patients with gallstones. Squares indicate control patients; *X*'s, patients with cholesterol stones; and diamonds, patients with pigment stones.

in both groups of patients with gallstones compared with control patients (Table). Thus, unlike in animal models of gallstone formation, no increase in free Ca^{++} or total calcium was observed in bile from patients undergoing treatment for gallstones.

COMMENT

Calcium plays a key role in many physiologic processes, including skeletal and myocardial muscle contraction, nerve conduction, blood coagulation, bone and tooth formation, and epithelial secretion and absorption. Consequently, the serum free Ca^{++} concentration is precisely controlled in humans to a value of 1.14 ± 0.13 mmol/L, and calcium is found in all body fluids at concentrations similar to or higher than that found in serum.[14]

Several anions in biologic fluids, including carbonate, phosphate, oxalate, free fatty acids, and bilirubin, contain calcium salts that are poorly soluble in aqueous solution.[7] When the solubility of any one of these salts is exceeded, the fluid is said to be supersaturated with that salt, indicating that precipitation is thermodynamically possible.[7] Saliva, pancreatic juice, and bile are all supersaturated with calcium carbonate,[7,8,15] and urine is often supersaturated with calcium oxalate under normal conditions,[16] leading to the formation of calcium calculi in these organs. While the prerequisite for calcium precipitation is therefore present in each of these organs, the fact that most humans never develop any type of stone emphasizes the importance of nucleating or antinucleating factors, which determine if and when precipitation occurs.[3-5,17]

A role for calcium precipitation in gallstone disease is supported by the finding that hyperparathyroidism (elevated serum free Ca^{++} and total calcium concentrations) is associated with an increased incidence of cholelithiasis[18] and by results of studies of animal models of both pigment[13,19] and cholesterol[20] gallstones. Oral calcium supplementation in prairie dogs results in an increased incidence of pigment gallstones,[21] while both dogs[13,19] and hamsters[22] fed lithogenic diets developed elevated biliary free Ca^{++} and total calcium concentrations early during pigment gallstone formation. Prairie dogs fed high-cholesterol diets developed cholesterol gallstones and an increased biliary calcium concentration,[20] and both stones and elevated calcium concentrations are potentiated by the administration of estrogen to these animals.[23]

Shiffman et al[24] reported increased Ca^{++} concentration in bile from patients with all types of gallstones when compared with control patients undergoing operation not related to biliary tract disease, usually gastric bypass for morbid obesity. These findings, however, have not been observed by others[25,26] or by us in the present study. Rather, free Ca^{++} and total calcium concentrations were decreased in gallstone-containing bile consistent with the reduced degree of bile concentration noted in these patients. There are several possible explanations for the discrepancy between our findings and those of Shiffman et al.[24] Fasting time before operation and selection of "control" patients cannot be adequately controlled. Fasting time may vary greatly from study to study or from control patients to patients with gallstones, and a uniform fasting period does not ensure similar residence time in the gallbladder, as patients with gallstone disease may have impaired motility (stasis). Certainly, it can be questioned whether patients with an eating disorder, such as morbid obesity, are appropriate controls for patients with gallstones, and we thus chose "normal" patients undergoing non–biliary tract abdominal surgery as controls in our study. In fact, the difference in conclusions between our study and that of Shiffman et al appears to reside with differences in the results obtained in control patients, not in those observed in patients with gallstones.

As already pointed out, calcium precipitation from biologic fluids and subsequent stone formation is an intermittent and most likely a transient event. Elevations in biliary calcium concentration might then also be transient. If this is the case, one would not expect differences in biliary calcium in patients undergoing operative treatment for symptomatic gallstones, as patients with gallstones may have asymptomatic cholelithiasis for 15 to 20 years or longer.[27] Sampling of bile would therefore be remote from the period of "lithogenicity," and transient increases might never or only rarely be observed. The few samples in this study that exhibited high biliary calcium values (Fig 4, bottom) might then be of interest, as they might represent bile that actually was "lithogenic" for calcium at the time of sampling.

Evidence for transient elevation of biliary calcium concentration during gallstone formation exists in the canine model of pigment gallstones. In this model, markedly elevated free Ca^{++} and total calcium concentrations are always observed after 6 weeks of lithogenic diet during sludge and pigment gallstone formation.[13,19] In contrast, Englert et al[28] did not observe elevations in biliary total calcium concentration after 3 months, when stones were well formed. Effects of a prolonged presence of gallstones in the gallbladder and changes that occur as a result of chronic inflammation may explain these time-dependent differences in bile composition, but correlation between the length of the gallstone disease, degree of histologic change, and biliary calcium levels is impossible in the clinical setting. Therefore, the final answer to the question of whether elevation of biliary calcium concentration leads to gallstone formation will require studies in animal models or in patients in whom gallstones are actively forming at the time of bile sampling.

Before discounting biliary calcium in gallstone pathogenesis because elevations of biliary calcium were not seen in our patients with gallstones, it is important to understand that saturation of any calcium salt depends on the product of both free ionized calcium and anion concentrations ($Ca^{++} \times \text{anion}$) in solution. Saturation can then be exceeded by increases in anion concentration, as well as by increases in calcium concentration.[7] Thus, a defect in gallbladder bile acidification has been hypothesized that would result in slower clearance of the calcium-sensitive anion, carbonate, from bile[29] and prolonged supersaturation of gallbladder bile with calcium carbonate.

Based on a lack of difference in gallbladder bile pH between groups in our study, we conclude that no significant defect in acidification of gallbladder bile exists in patients with gallstones during this stage of their disease. Yet, the reduction in the degree of concentration and the slight decrease in the acidification of gallbladder bile we observed in patients with gallstones have implications for calcium precipitation. More than half of the bile samples we studied were supersaturated with calcium carbonate at the time of sampling (Fig 2), indicating that precipitation is thermodynamically possible in both normal and abnormal gallbladder bile for hours after fasting begins. Decreased concentration and acidification of gallbladder bile results in higher calcium carbonate SIs[8] and lower concentrations of bile salts and phospholipids, components of bile that are important for the solubilization of calcium-sensitive anions, such as unconjugated bilirubin.[30] Therefore, our studies neither prove nor disprove that precipitation of calcium from bile is important in gallstone formation. Considering that bile is frequently supersaturated with at least one calcium salt for considerable periods, these results suggest that nucleating and antinucleating factors are exceedingly important.

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Cardiac Risk in Vascular Surgery

The Oral Dipyridamole-Thallium Stress Test

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• The value of the oral dipyridamole-thallium stress test in identifying patients at high risk of myocardial infarction after vascular procedures has not been documented. We studied prospectively 46 patients who underwent an oral dipyridamole-thallium stress test before undergoing vascular operations. Twenty patients (43%) had a positive test result, defined by a thallium defect with reperfusion, while 26 patients had a negative test result. Myocardial infarctions were documented postoperatively in 5 (25%) of 20 of the group with positive results and 1 (4%) of 26 of the group with negative results. Three of the six myocardial infarctions were clinical; all three were in the group with positive results. No correlation was identified between dipyridamole-thallium stress test results and clinical cardiac history. A positive dipyridamole-thallium stress test result is a more sensitive predictor of postoperative myocardial infarction than ejection fraction or history of coronary artery disease. The oral dipyridamole-thallium stress test is as useful as the intravenous test in this setting.

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Coronary artery disease (CAD) is very prevalent in patients requiring peripheral vascular operations. Sixty percent have at least one significant coronary artery stenosis (>70% diameter reduction) when subjected to routine angiography.[1] Myocardial infarction (MI) following surgery is reported in 2% to 15% of patients, depending on methods used for detection and selection criteria.[2] Since the event is "silent" in over half of the cases, many infarctions go undetected in large retrospective studies.[3] However, MI remains a major cause of immediate and late mortality in this patient population.

Efforts to identify the high-risk patients can result in modification of the operative approach or a prophylactic myocardial revascularization before the vascular procedure. Methods relying on clinical history, multivariate risk-factor analysis, or estimation of ejection fraction (EF) by radionuclide ventriculography are helpful, but lack enough sensitivity. Routine catheterization provides the best delineation of the extent of CAD, but is invasive and expensive, and the anatomic information yielded is hard to correlate with the exact surgical risk. Stress testing has suffered from the inability of several vascular patients to exercise adequately for a meaningful test. Pharmacologic coronary vasodilatation with dipyridamole, combined with thallium imaging, is, however, particularly well-suited for these patients, and has been proposed as a good screening test.[4-6]

The majority of dipyridamole-thallium stress tests (DTSTs) reported have used the intravenous form of the drug, which is still not available in the United States for general use. Some encouraging reports on the use of oral dipyridamole prompted us to evaluate the oral DTST as a screening test for identifying patients at high risk for MI following peripheral vascular procedures.[7-9]

PATIENTS AND METHODS

One hundred veterans consecutively admitted for elective major vascular reconstructions over a 10-month period, from August 1988 to May 1989, were evaluated by a cardiologist based on history, physical examination, and a 12-lead electrocardiogram. Forty-eight patients underwent vascular procedures without a DTST for a variety of reasons. These included patients with severe symptomatic heart disease requiring coronary angiography, recent coronary artery bypass grafting or catheterization within the previous year, limb-threatening severe ischemia requiring urgent revascularization, a planned simple extra-anatomic bypass, uncooperative patients with psychotic disorders, and a few patients with scheduling problems.

The remaining 52 patients underwent a DTST according to a protocol adopted from the report of Taillefer et al.[7] The patients ate nothing by mouth the morning of the test and had no xanthines for 24 hours previously. A 12-lead electrocardiogram was obtained and an intravenous line started. An oral dose of 400 mg of dipyridamole, in pulverized form, was then administered, and the patients were monitored closely subsequently. At 40 minutes, 88.8 MBq of thallium 201 was infused to correspond with the peak level of dipyridamole.[8] Serial imaging was then obtained immediately and after 3 hours in the anterior, 45°, and 70° left anterior oblique projections. After the first set of myocardial images, an intravenous infusion of 125 mg of aminophylline dihydrate was given to reverse the effects of dipyridamole in all patients. One patient had his test canceled because he developed severe chest pain after receiving dipyridamole, requiring immediate administration of aminophylline; he did not suffer a myocardial infarct. This patient is not included with the 52 patients; he subsequent-

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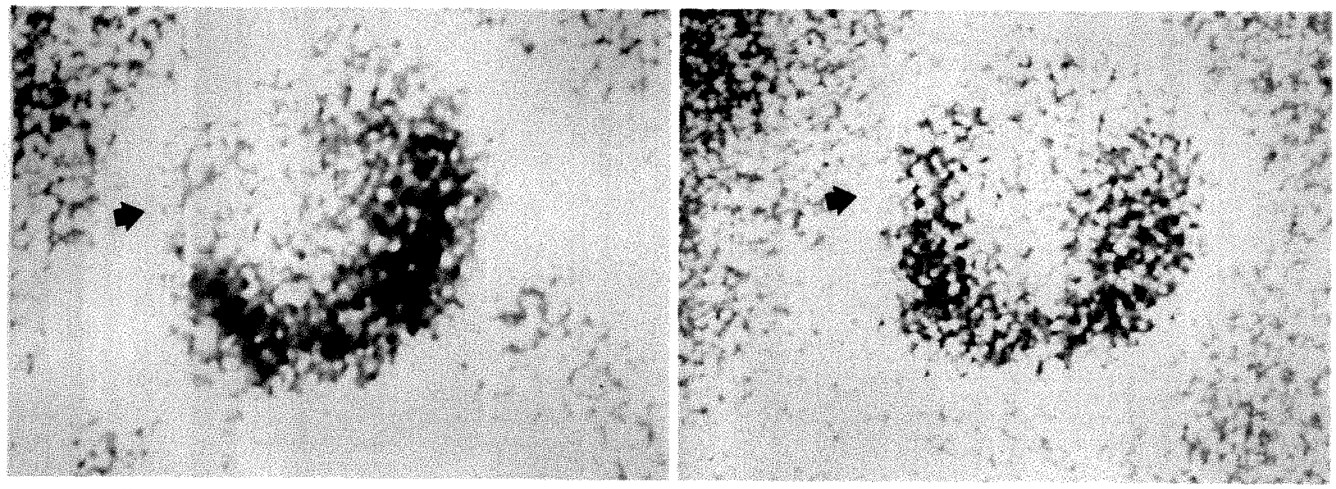

Fig 1.—Positive dipyridamole thallium stress test result. Left, A defect in the area of the septum is seen (arrow). Right, The same area reperfuses on the delayed scan.

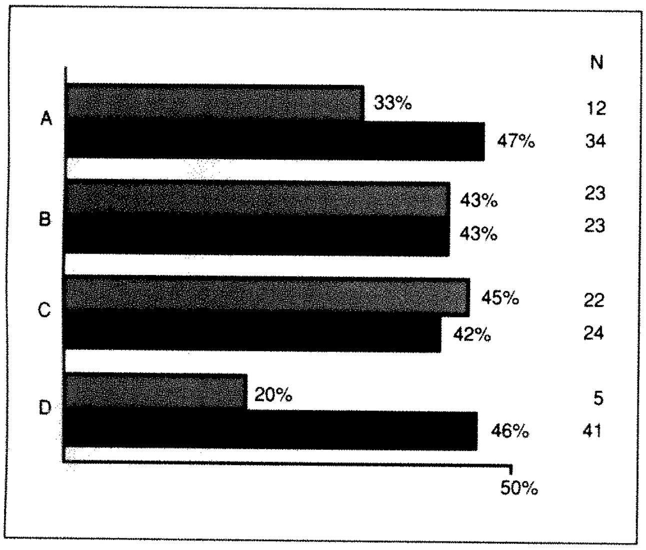

Fig 2.—Incidence of positive dipyridamole thallium stress test results among various patient groups. No clinical factor was predictive of the results of the test; only previous myocardial revascularization seemed to predict a negative test result. Shaded bars represent presence of a condition; closed bars, absence of a condition; A, diabetes; B, hypertension; C, coronary artery disease; D, percutaneous coronary angioplasty or coronary artery bypass grafting; and N, number of patients in each group.

ly underwent an uneventful mesenteric artery bypass. Other side effects encountered included nausea in four patients, mild chest pain in two patients, and a "hot" feeling in one patient. No infarctions, arrhythmias, or deaths resulted from the test. All side effects resolved promptly with aminophylline.

The test results were reviewed by a cardiologist and a nuclear medicine staff physician. The test result was considered positive if there were one or more defects on the initial scan that showed evidence of reperfusion on the delayed images. Normal scans or fixed defects were classified as negative test results. An example of a positive test result with a reperfusion defect in the area of the septum is shown in Fig 1.

The surgeon and anesthesiologist were aware of the test result when patients underwent their vascular procedures. All patients were monitored intraoperatively with an arterial line. A pulmonary artery catheter was used in all patients with a positive test result and almost all patients with a negative test result. Twelve lead electrocardiograms were obtained routinely after operation in the recovery room and the next day. Three sets of creatinine phosphokinase isoenzymes were also measured routinely in the first 36 hours after operation. Routine tests were not performed later, because the incidence of silent perioperative MIs decreases significantly after the first postoperative day; however, if clinically indicated they were repeated as often as necessary.[3] Only documented MI or cardiac death within 30 days of surgery were considered end points. Episodes of angina, which are of no long-term clinical significance, and congestive heart failure, which is difficult to evaluate after perioperative volume loading, were not considered in comparisons of cardiac morbidity.

Six of the 52 patients, three with a positive test result and three with a negative test result, had their operation canceled for reasons unrelated to the DTST. These were nonreconstructible peripheral disease, metastatic lung cancer, an EF of 20%, and extensive generalized aneurysmal disease in one patient each. Two patients refused the operation after evaluation, one after a complicated prophylactic coronary artery bypass.

RESULTS

Forty-six patients who had a DTST and underwent 47 vascular procedures form the basis of this report. There were 29 aortic reconstructions, 16 infrainguinal bypasses, one femorofemoral bypass, and one resection of a femoral pseudoaneurysm. The patients were divided into two groups: 20 patients with positive test results and 26 with negative results. The incidence of positive test results in this population was 43%, which correlates well with the 35% to 50% incidence reported in the literature describing the intravenous test.[4,5,10,11] Six patients with a positive test result had a coronary angiography. All but one had severe coronary disease (>70% diameter reduction). Three patients had diffuse nonreconstructible disease. One patient had a percutaneous coronary angioplasty, and another had coronary artery bypass grafting. Since neither had a repeated DTST, they were analyzed as part of the group with positive results. Neither had an MI.

The DTST did not correlate well with any factor from the clinical profile of the patients (Fig 2). No factor was predictive of the test results. However, all four patients with a previous cardiac artery bypass grafting, from 2 to 9 years previously, had negative test results. One patient with a percutaneous coronary angioplasty 5 years earlier had a positive test result, for an incidence of positive test results of 20% in patients with prior myocardial revascularization.

The two groups were very similar in all risk factors analyzed (Table 1). Slightly more aortic procedures were performed in the group with negative DTST results (not significant). Sixteen patients had EF determined by multiple uptake gated acquisition scan. The mean EF was similar between groups, and none was lower than 40%.

Table 1.—Risk Factors Among Patients With Positive or Negative Dipyridamole-Thallium Stress Test Results*

	Positive	Negative
Mean age, y	63.5	63.1
Smoking	100	100
Hypertension	50	50
Diabetes	20	31
CAD	50	46
PTCA or CABG	15	15
Aortic procedures	55	69
EF, mean (range)	59 (53-68)	58 (40-71)

*All values are percentages except for age. CAD indicates coronary artery disease; PTCA, percutaneous coronary angioplasty; CABG, coronary artery bypass grafting; and EF, ejection fraction.

Table 2.—Incidence of Myocardial Infarction or Cardiac Death by Dipyridamole-Thallium Stress Test Results*

Study, Year	Positive Result, No. (%)	Negative Result, No. (%)
Boucher et al,[4] 1985	4/16 (25)	0/32
Cutler and Leppo,[5] 1987	8/31 (26)	0/60
Leppo et al,[6] 1987	14/42 (33)	1/47 (2)
Sachs et al,[10] 1988	3/14 (21)	0/26
Present series	5/20 (25)	1/26 (4)

*The test was administered intravenously in all the studies listed except the present series, in which it was administered orally.

Six patients had documented postoperative MIs, four after aortic reconstruction and two after femorotibial bypass. Five (25%) of 20 patients with positive DTST results had an MI and only one (4%) of 26 patients with negative DTST result had an MI. This difference was compared using the z statistic yielding a value of 2.11, and a one-tailed P value of .017, which is statistically significant (Fig 3). All three clinical MIs, including a fatal one, were in the group with positive DTST results. There was one death in the group with negative results due to a pulmonary embolus. The difference between the two groups would have been even more pronounced if the two patients who had myocardial revascularization after positive DTST results had been excluded from the group with positive results. Since neither had an MI, and since in all likelihood their DTST results would have been negative if repeated, their inclusion in the group with positive results has resulted in a slight underestimation of the MI risk in patients with positive DTST results.

Clinical history and EF were not useful in predicting MI after operation. Three patients who developed an MI, including the fatal one, had no previous clinical markers of CAD. Preoperative ejection fraction by multiple uptake gated acquisition scan was available for three of the six patients who had MIs, and was normal for all three (60%, 61%, and 67%).

When compared with previously reported series that used similar end points, our results with the oral DTST are very similar to the results obtained by other investigators using the intravenous test (Table 2). Using MI or cardiac death as the clinical end point, the combined data yield a sensitivity for the test of 95% and a specificity of 68%. The similar figures for our own data are 83% and 62%, respectively.

COMMENT

What constitutes an adequate cardiac evaluation in patients about to undergo a peripheral vascular operation remains controversial. There is uniform agreement that CAD is widespread in this patient population, and is the direct cause of postoperative and late morbidity and mortality.

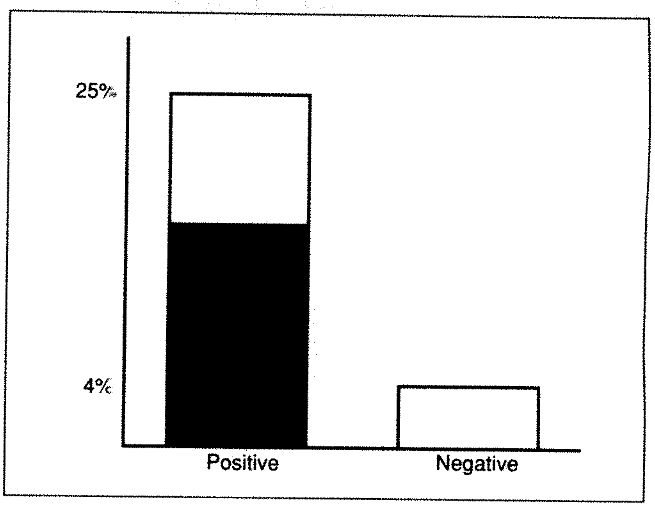

Fig 3.—Incidence of postoperative myocardial infarction among the groups with positive (5 [25%] of 20) and negative (1 [4%] of 26) results on the dipyridamole thallium stress test (DTST). Closed bars indicate clinical and open bars, "silent" myocardial infarctions. All the clinical and the only fatal myocardial infarctions were in the group with positive results. The difference is significant ($P = .017$).

The administration of dipyridamole results in maximal coronary vasodilatation equivalent to that produced by exercise, without the deleterious effects of increased oxygen consumption and severe tachycardia. Combined with thallium 201 imaging, it provides excellent information about the presence of a scar from an old MI, or ischemic myocardium at risk for a myocardial infarct.[12] The test was first introduced by Albro and coworkers[13] in 1978 and found to be safe and minimally invasive. When compared with angiography, it reliably identifies significant stenoses with a sensitivity of approximately 90% and a specificity of 70%.

It was only logical to use this test in the patients scheduled for vascular surgery. All the evidence suggests that these patients should undergo stress testing to uncover occult CAD, but the majority are unable to exercise.[14] The DTST provides a very good simulation of myocardial stress. The first report by Boucher et al[4] in 1985 was followed by others with remarkable similarity in results. These studies demonstrated the effectiveness of DTST in predicting MI or death after peripheral vascular procedures with a very high sensitivity but a low specificity.[5,6] However, widespread use was limited by the unavailability of intravenous dipyridamole. Reports by Taillefer et al,[7] Homma et al,[8] and Aksut et al[9] suggested that the test could be performed effectively with oral dipyridamole with less serious side effects. Only headache and nausea are more frequent with the oral dose, whereas the incidence of angina is significantly reduced.

We evaluated the oral test in the preoperative screening of peripheral vascular patients and found that redistribution of thallium occurs in 43% of the tests and defines a group at 25% risk of developing an MI or cardiac death after operation when routine surveillance is employed. These numbers are nearly identical to results reported with the intravenous DTST. This should then provide a safe and easily available screening test before vascular surgery. Our low incidence of side effects was probably due to the routine use of aminophylline to reverse the effect of dipyridamole. Since the reversal of that effect might actually even be desirable before the second set of images are obtained, we recommend using aminophylline routinely following the initial scans.

The high sensitivity of DTST is one of its best features. A negative test result strongly suggests the absence of any myocardium at risk, and surgery can proceed without any further elaborate evaluation. However, a lingering concern with this test is its low specificity. Attempts to improve this aspect will result in a much higher positive predictive value, making it a very valuable clinical tool. Reports of combining DTST with exercise, selective use of the test according to some clinical criteria, or developing a quantitative index of thallium redistribution are encouraging, but require further validation.[11,15,16]

Because of the low specificity, the course of action to be taken when the DTST result is positive is not entirely clear. This decision should presently be left to the clinical judgment of the surgeon and the individual situation of the patient. Proceeding with a more limited operation, intraoperative monitoring of ischemia, eg, with transesophageal echocardiography, or angiography with prophylactic myocardial revascularization are but some of the options. The significant risk and cost of angiography and coronary revascularization should be weighed against the benefits expected to be derived and the risk of delaying the peripheral vascular intervention. Larger studies are needed to delineate the most appropriate management option in this situation. A uniform approach cannot be presently recommended from available data.

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Surgical Anatomy Question

Q The ribbon or strap muscles are supplied by the ansa hypoglossus, a branch of the 12th cranial nerve. [True or False?]

A [False] These ribbon (infrahyoid) muscles are supplied by the anterior rami of cervical nerves 1, 2, and 3 via the hypoglossal nerve and the ansa hypoglossi.[1]

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The Natural History of Intimal Flaps in a Canine Model

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• The natural history of arterial intimal flaps has not been well defined. This study characterizes the natural history of unrepaired intimal flaps. Thirty-nine 1-, 2-, and 3-mm hemispheric, distally based intimal flaps were made in 4- to 5-mm diameter canine femoral and carotid arteries. Twenty arteries had 2- and 3-mm intimal flaps and were monitored for short-term arterial thrombosis and flap extension. Nineteen had 1- and 2-mm intimal flaps and were monitored for thrombosis, long-term development of neointimal hyperplasia, arterial stenosis, and persistence of the flap. While 40% of the arteries with 3-mm intimal flaps developed thrombosis in 3 to 5 days, only 3% of the arteries with 1- or 2-mm intimal flaps developed thrombosis. Most 1- or 2-mm intimal flaps resolved and the subsequent development of neointimal hyperplasia or arterial stenosis was minimal. Arteries with hemodynamically significant stenoses from intimal flaps warrant repair, while arteries with smaller intimal flaps may not require repair.

(*Arch Surg.* 1990;125:1614-1616)

Intimal flaps may develop in arteries following trauma, catheterization, or operation. Some intimal flaps result in arterial occlusion, while others have benign courses and do not produce any significant arterial lesions. This study evaluates the natural history of intimal flaps. A better understanding of the behavior of intimal flaps may be useful in the clinical management of patients with these lesions.

MATERIALS AND METHODS

Intimal flaps of 1, 2, or 3 mm encompassing 50% of the arterial circumference were made in thirty-nine, 4- to 5-mm-diameter canine femoral and carotid arteries. The arteries were studied 3 to 5 days (early outcome) and 2 months (late outcome) following surgery.

Pentobarbital sodium was administered intravenously to anesthetize the dogs. The dogs were intubated and given inhalation anesthesia. The necks and groins were antiseptically prepared and draped. A midline neck incision was used to gently dissect the common carotid arteries. The common femoral arteries were isolated through bilateral groin incisions.

One hundred units of heparin sodium per kilogram of body weight was given intravenously. After 5 minutes, the first artery was clamped with atraumatic vascular clamps. A 15-mm longitudinal arteriotomy was made. A transverse incision was made in the posterior intima encompassing half of the arterial circumference. A Penfield dissector was then used to gently separate the intima from the media to create either a 1-, 2-, or 3-mm hemispheric, distally based intimal flap (Figs 1 and 2). Flap length was measured in its center using a surgical ruler. The artery was irrigated with heparinized saline and closed with a running 6-0 polytetrafluoroethylene suture.

In a similar manner, intimal flaps were constructed in the remaining carotid and femoral arteries. Specimens harvested 3 to 5 days after surgery had 2-mm intimal flaps constructed in one carotid and one femoral artery and 3-mm intimal flaps constructed in the other carotid and femoral arteries. Specimens harvested 65 days after surgery had 1-mm intimal flaps constructed in one carotid and one femoral artery and 2-mm intimal flaps constructed in the other carotid and femoral arteries.

The neck and groin incisions were closed using running 2-0 and 3-0 polyglactin sutures. The incisions were antiseptically dressed.

The 20 early-outcome arteries were harvested 3 to 5 days following creation of the flaps. Ten of these arteries (group 1) had 2-mm intimal flaps and 10 (group 2) had 3-mm intimal flaps. These arteries were ligated, excised, and opened longitudinally along the arterial suture line. They were studied for occlusion, thrombus formation, and flap extension.

The 19 late-outcome arteries were pressure-perfused and fixed in 10% buffered formaldehyde solution (mean period of fixation, 65 days). Nine of these arteries (group 3) had 1-mm intimal flaps and 10 (group 4) had 2-mm intimal flaps. These arteries were sectioned transversely.

The late-outcome arteries were examined for size of intimal and medial area, percent of luminal reduction from any present intimal flap, percent of luminal reduction from neointimal hyperplasia, and arterial occlusion. To measure these parameters, the histologic slides were projected onto a digital reader, and a drawing of the lumen, intima, basement membrane, media, and adventitia was made. This drawing was placed on a computer grid, and the outlines of each of these layers were traced using a transducer. A computer then calculated the individual circumferences and areas of each of these layers.

In addition, angioscopy was done in eight early-outcome and eight late-outcome arteries to qualitatively assess the intimal flaps and any resulting luminal stenoses.

The data were analyzed using a statistical software t test (SAS, SAS Institute Inc, Cary, NC) and Fisher's Exact test. A P value of less than or equal to .05 was considered statistically significant.

RESULTS

Figure 3 shows an artery 5 days after surgery that contains a 2-mm intimal flap. As can be seen, this intimal flap resulted in approximately 50% luminal stenosis. Figure 4 shows an artery 5 days after surgery that contains a 3-mm intimal flap. This flap resulted in approximately 75% luminal stenosis.

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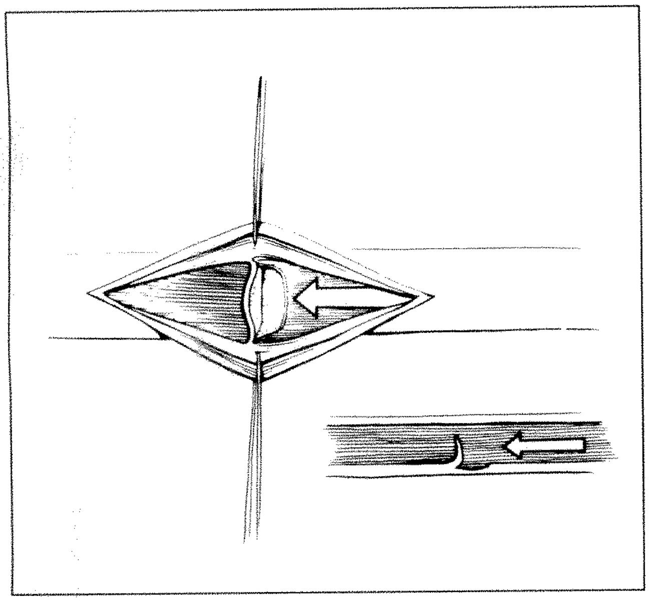

Fig 1.—Longitudinal view of an artery with an experimental intimal flap.

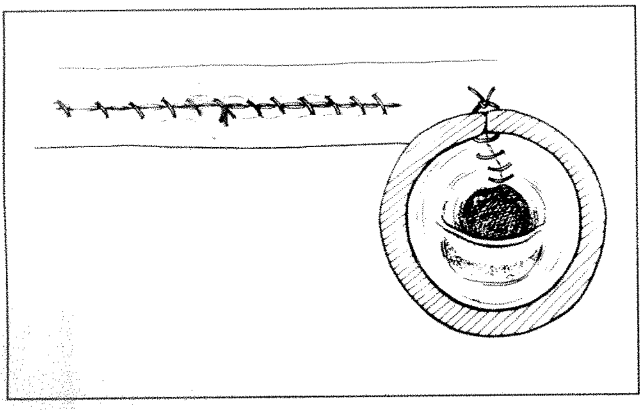

Fig 2.—Cross-sectional view of an artery with an experimental intimal flap.

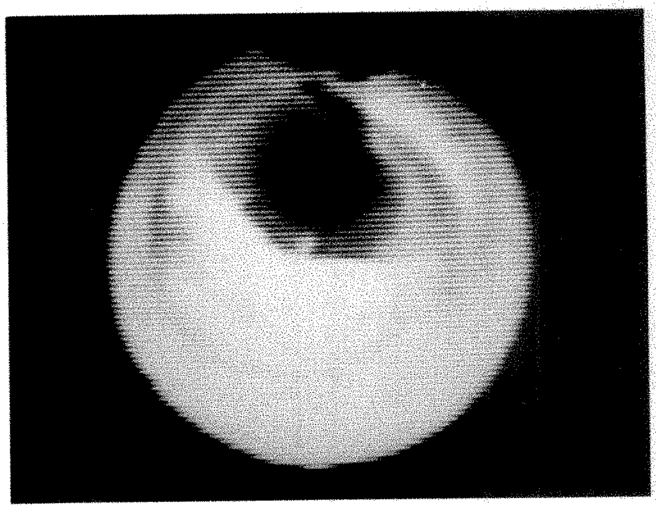

Fig 3.—Angioscopic photograph of an artery with a 2-mm, hemispheric intimal flap. This results in 50% luminal stenosis.

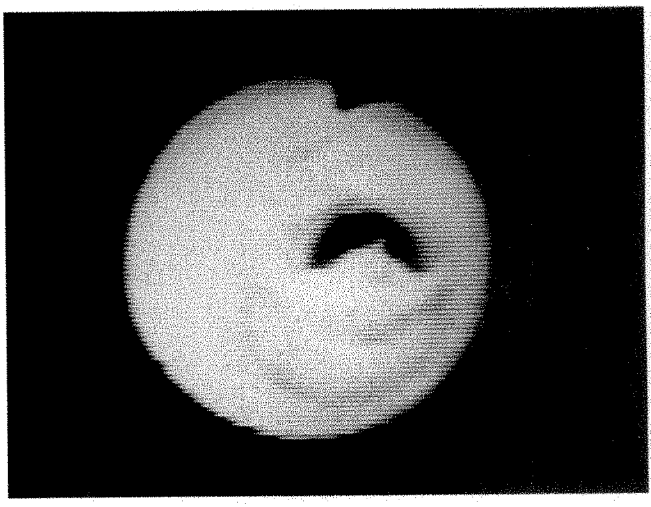

Fig 4.—Angioscopic photograph of an artery with a 3-mm, hemispheric intimal flap. This results in 75% luminal stenosis.

In the early-outcome arteries, one (10%) of 10 with 2-mm intimal flaps (group 1) occluded, while four (40%) of 10 with 3-mm intimal flaps (group 2) occluded. No thrombus was present in any of the 15 remaining patent arteries. None of the intimal flaps had extended. No group 3 arteries with 2-mm intimal flaps or group 4 arteries with 1-mm intimal flaps occluded during this study. The difference between the occlusion rate of all arteries with 2-mm intimal flaps (one of 20) and the occlusion rate of arteries with 3-mm intimal flaps (four of 10) was statistically significant ($P = .031$ by Fisher's Exact test).

The late-outcome arteries were evaluated for the long-term effects of 1- and 2-mm intimal flaps. Only three of these 19 arteries had persistent intimal flaps 65 days after surgery, and seven of the 19 arteries were completely normal. The remaining arteries had minimal evidence of neointimal hyperplasia. In the three arteries with persistent intimal flaps, stenosis caused by the flaps produced luminal reductions ranging from 0.2% to 0.9%. Total luminal reduction from neointimal and myointimal hyperplasia was 3.85% ± 2.07% (SD) in group 3 (1-mm intimal flaps) arteries and 8.31% ± 3.84% in group 4 (2-mm intimal flaps) arteries. None of these arteries showed thrombus at harvest. Arteries in groups 3 and 4 showed no statistically significant differences in intimal and medial thickness, intimal and medial area, percentage of luminal reduction from neointimal hyperplasia, or presence of arterial intimal flaps ($P > .30$) (Table). In late-outcome arteries in which angioscopy was done, only minimal irregularities were seen.

COMMENT

Isolated intimal flaps represent 10% of traumatic arterial injuries.[1] Intimal flaps may also result from arterial catheterization and angioplasty. Small, residual intimal flaps sometimes develop following endarterectomy and other vascular operations. Many of these intimal flaps are benign and do not produce significant sequelae. Many surgeons have recommended an aggressive surgical approach to the repair of all arterial defects.[2-10] However, this experimental study and a number of recent clinical studies[11-21] have shown that small intimal flaps may resolve spontaneously and that some of these lesions may be managed safely without surgery. Although this experimental study with precisely made intimal flaps does not match the range of clinical injuries that occur, it may lead to guidelines for determining which injuries warrant repair.

In a clinical study of arterial intimal flaps, Sawchuk et al[11]

Comparison of Arterial and Luminal Parameters for Late-Outcome Arteries With Intimal Flaps*

	Group 3, 1-mm Flaps	Group 4, 2-mm Flaps
Average intimal thickness, mm	1.28±0.48	1.13±0.48
Average medial thickness, mm	2.91±0.36	2.60±0.28
Average intimal area, mm²	1.32±0.74	2.94±1.44
Average medial area, mm²	8.12±1.37	8.15±0.65
Intimal flap area, mm²	0.22±0.15	0.10±0.10
Luminal reduction resulting from intimal flaps %	0.11±0.09	0.09±0.09
Total luminal reduction, %	3.85±2.07	8.31±3.84

*Data are means ± SD.

reviewed the duplex ultrasound study results of 79 patients who had undergone carotid endarterectomies. All of these carotid arteries had been assessed using intraoperative B-mode ultrasonography. Eighteen carotid arteries had small, residual intimal flaps. Three of the intimal flaps in this study were 1-mm, distally based, internal carotid artery flaps, and seven were 1- to 3-mm, distally based, external carotid artery intimal flaps. The remaining intimal flaps were 1- to 3-mm, proximally based, common carotid artery intimal flaps. Sixteen of 18 patients with these residual, minor, arterial intimal flaps had completely normal carotid arteries at the time of their first postoperative duplex ultrasound examinations, which documented healing of the flaps. During follow-up (mean interval, 32 months), there was no difference between the occlusion rates of arteries with small, residual intimal flaps and those of arteries without flaps. It should be emphasized that these intimal flaps were small, trapdoor arterial intimal flaps that encompassed only small portions of the arterial lumina. However, this study does indicate that human intimal flaps may resolve without producing thrombosis or stenosis.

Dennis et al[12] and Frykberg et al[13-14] have reported the results of nonoperative management of asymptomatic arterial intimal flaps following penetrating trauma in the proximity of major limb arteries. All of their studies had similar results. In one study,[12] 12 arteries with arterial intimal flaps diagnosed using arteriography were managed nonoperatively. Nine of these intimal flaps were evaluated by follow-up arteriography. Six of these nine intimal flaps resolved completely. Two of the nine intimal flaps got smaller. One of the nine arteries with intimal flaps developed a pseudoaneurysm that was repaired electively. Three of the 12 arteries with intimal flaps were followed up clinically. Two patients remained asymptomatic, but one developed a pseudoaneurysm that was also repaired electively. These authors conclude that clinically occult arterial injuries do not necessarily mandate surgery and, thus, may not need to be found because the natural course of the vast majority is to resolve or exist benignly. The authors did not measure the percentage of luminal reduction caused by intimal flap–induced stenosis, and they repaired all symptomatic lesions.

We are not aware of any large-animal studies investigating the natural history of intimal flaps. Glover et el[22] reported on the natural history of traumatic intimal tears in rats followed up for up to 48 weeks. None of these arteries with intimal tears developed thrombosis, although some medial disorganization and hyperplasia were present in the arteries at the sites of the intimal lesions.

This study documents the natural history of surgically created intimal flaps in an experimental large-animal model. Intimal flaps of 1 or 2 mm had generally benign courses in arteries measuring 4 to 5 mm in diameter. While occlusion with approximately 75% luminal stenosis occurred in four (40%) of the 10 arteries with 3-mm intimal flaps, occlusion with 50% luminal stenosis occurred in only one (3.3%) of 30 arteries with 1- and 2-mm intimal flaps. Six weeks after surgery, luminal stenosis resulting from neointimal hyperplasia, myointimal hyperplasia, and residual intimal flaps was minimal, with a mean luminal reduction of 6.20% ± 2.25% in the 19 arteries followed up for this length of time. Only three intimal flaps persisted on histologic examination, and seven of the arteries were completely normal.

These preliminary data suggest that 4- to 5-mm-diameter arteries with intimal flaps of 3 mm or larger and luminal area reduction of at least 75% have a high rate of early thrombosis and warrant repair. Arteries with smaller intimal flaps may not require repair. It is important to realize that this study only evaluated the effects of the intimal flap itself. In clinical practice, additional arterial damage may result from blast injury and arterial contusions. However, recent clinical data[12-14] confirm that many isolated injuries of arterial intimal flaps spontaneously improve or resolve and do not require surgical intervention.

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The Effect of Intestinal Resection and Urogastrone on Intestinal Regeneration

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• Intestinal regeneration in patched intestinal defects is enhanced by both intestinal resection and urogastrone. Our aim was to determine if these two stimuli have synergistic effects. Ileal defects were patched with colon serosa in 45 rabbits. Group 1 (n = 11) were control subjects; group 2 (n = 12) underwent 50% intestinal resection; group 3 (n = 11) received urogastrone (1.5 μg/kg per hour subcutaneously); and group 4 (n = 11) underwent intestinal resection and received urogastrone. Animals were killed at 7 and 14 days. Intestinal resection had the greater effect on epithelialization. Urogastrone inhibited contraction and intestinal resection did not. Both intestinal resection and urogastrone increased proliferative activity. Combining intestinal resection and urogastrone did not have a synergistic effect on epithelialization and diminished the effect of urogastrone on proliferation and contraction. These findings suggest that intestinal resection and urogastrone stimulate epithelialization via similar mechanisms and that urogastrone would not enhance regeneration during intestinal adaptation.

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Several surgical procedures have been evaluated for improving absorptive function in patients with the short bowel syndrome.[1] These include techniques for retarding intestinal transit and increasing intestinal surface area. While transplantation of the small intestine is an obvious method for increasing intestinal surface area, the regenerative capacity of the intestine is also being explored as a means of increasing the absorptive surface of the intestine.

Intestinal regeneration occurs in full-thickness intestinal defects patched with adjacent colon serosal surface. The growth of new intestinal mucosa, termed *neomucosa*, occurs by proliferation of epithelial cells in the crypts of the mucosa lining the defect and migration of cells across the patched defect. The patched defect also contracts due to a currently undefined mechanism that might involve the subepithelial tissues. Thus, the potential increase in intestinal surface area that can be achieved by intestinal patching is influenced by the rate of epithelialization, extent of contraction, and quantity of patching surface available.

Several factors affect the rate and extent of intestinal regeneration.[1] Intestinal resection performed at the time of intestinal patching increases mucosal proliferative activity and thus increases the rate of neomucosal growth.[2] Urogastrone (human epidermal growth factor) administration increases both proliferative activity and the rate of epithelial cell migration.[3-5] Furthermore, it inhibits contraction of the patched defect. It is unclear whether the stimulation of proliferative activity by these two agents occurs via the same mechanism.[6] Since intestinal patching in the clinical setting would most likely be performed in patients with adjacent intestinal resection, the purpose of this study was to determine the combined effects of intestinal resection and urogastrone on neomucosal growth.

MATERIALS AND METHODS

Forty-five male New Zealand white rabbits (weighing 2.3 to 3.3 kg) had two 2 × 5-cm ileal defects patched with the adjacent colon serosal surface. Group 1 (n = 11) comprised control subjects. Group 2 (n = 12) rabbits underwent resection of 50% of the small intestine, maintaining intestinal continuity. Group 3 (n = 11) rabbits had mini-osmotic pumps (Alzet model 2ML1 or 2ML2, Alza Corp, Palo Alto, Calif) placed subcutaneously. Lyophilized recombinant urogastrone (Chiron Corp, Emeryville, Calif) of 95% purity was infused continuously at a rate of 1.5 μg/kg per hour. Group 4 (n = 11) rabbits underwent both 50% intestinal resection and urogastrone infusion. Animals in each group were killed at 7 and 14 days. Neomucosal growth was determined by gross and microscopic measurements. Tissue ornithine decarboxylase (ODC) activity and crypt cell production rate (CCPR) were measured to assess proliferative activity. Neomucosal function was evaluated by measuring disaccharidase activity.

Operations were performed after an overnight fast using sterile techniques. Anesthesia was achieved with intramuscular ketamine hydrochloride (35 mg/kg) and xylazine hydrochloride (7 mg/kg). Intestinal patching was performed by making two 5-cm incisions on the antimesenteric border, beginning 10 cm and 20 cm proximal to the ileocecal junction. The serosal surface of adjacent colon was apposed to the cut edge of the defect with a continuous inverting 4-0 silk suture, creating a 2 × 5-cm serosal patch exposed to the lumen of the

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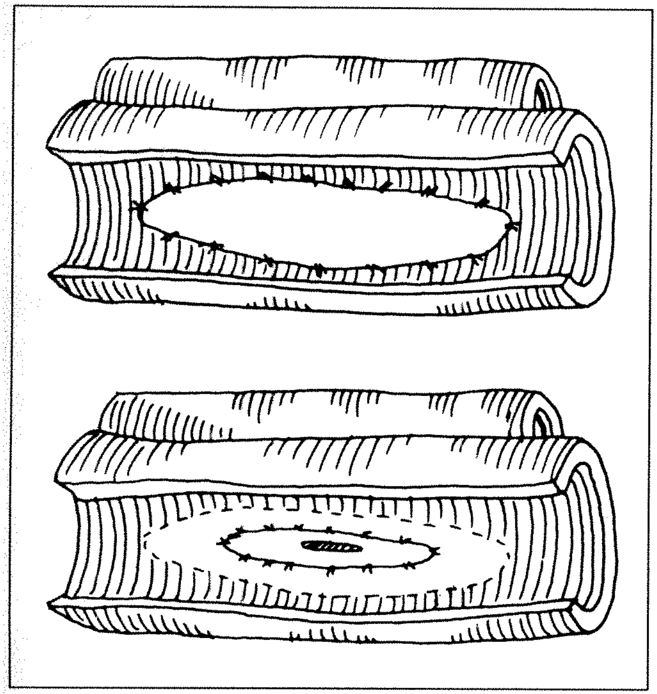

Fig 1.—The regenerating area within the suture line contracts between operation (above) and death (below). Coverage of the patched defect with neomucosa represents epithelialization; a small defect is shown. (from Thompson et al[16]).

small intestine. Group 2 and 4 animals underwent a 50% intestinal resection ending 30 cm proximal to the ileocecal junction, and continuity was maintained with a one-layer end-to-end anastomosis. In groups 3 and 4, a mini-osmotic pump containing urogastrone was placed subcutaneously lateral to the incision. The animals received perioperative ampicillin and supplemental subcutaneous fluid until resuming oral intake on the second postoperative day. The rabbits were active, ate normally, and maintained body weight during the study. Aspiration of pumps at necropsy confirmed complete infusion.

At the time the animals were killed, the size of the intestinal patch and any nonepithelialized area within the nonabsorbable suture line was determined by measuring the transverse and longitudinal diameters and calculating the area of the ellipse ($\pi r_1 r_2$). Epithelialization refers to the percentage of the defect covered with neomucosa (Fig 1). Contraction was calculated by determining the patched area at death and expressing it as the percentage of the initial defect size (2×5 cm). Samples of neomucosa were stained with hematoxylin-eosin. Measurements of villus height were taken in 10 intact axially oriented villi in each specimen with the aid of an eyepiece micrometer.

Crypt cell production rate was determined using the metaphase arrest technique with intraperitoneal vincristine sulfate (1 mg).[7] The mucosal samples were fixed in Carnoy's fixative, hydrolyzed in acid at 60°C for 5 minutes, and stained with Schiff's reagent. The crypts were dissected free using a dissecting microscope. Samples of crypts were transferred to a glass slide in 15% glacial acetic acid and squashed for determination of the number of metaphases per crypt in a minimum of 10 crypts. Crypt cell production rate was calculated assuming a linear accumulation for 2 hours. Activity of ODC was determined by a radiometric technique in which the amount of carbon 14 dioxide liberated from carbon 14 dioxide–labeled ornithine was estimated.[8] Ornithine decarboxylase activity was expressed in picomoles of carbon dioxide per milligram of protein per 30 minutes per patch. Disaccharidase activity in the neomucosa was determined according to the method of Dahlquist[9] and expressed in micromoles of glucose per gram of protein per minute.

Data are expressed as mean ± SD. Analysis of variance and the Bonferroni-corrected t test were used for comparisons, with $P<.05$ indicating significance.

RESULTS

Epithelialization of the patched defect was significantly greater in groups 2, 3, and 4 compared with control animals at both 7 and 14 days (Fig 2). Resection alone and resection and urogastrone resulted in greater epithelialization than urogastrone alone. Urogastrone inhibited contraction of the patched defect, while resection resulted in greater contraction than that seen in control and urogastrone-treated animals 7 days after operation. Neomucosal surface area was greater in groups 2, 3, and 4 than in control animals at 7 days but was similar at 14 days. Villus height was significantly less in the control animals than in the experimental groups at 7 days but was similar at 14 days.

Proliferative activity, as determined by CCPR and ODC activity, was increased by resection and urogastrone but the pattern of this increased activity was different (Fig 3). The crypt cell production rate was significantly lower in control animals than in the other three groups at 7 days. However, at 14 days, CCPR in control animals was significantly greater than in resected animals, suggesting a delayed proliferative response compared with the resected animals. Crypt cell production rate in urogastrone-treated animals was significantly greater than that in all other groups at 14 days. Ornithine decarboxylase activity was significantly reduced in control animals at 7 days but was similar among all four groups at 14 days.

Maltase activity was lowest in the neomucosa of control animals at 7 days but sucrase activity was similar (Fig 4). At 14 days, maltase and sucrase activity were greatest in the urogastrone-treated animals.

COMMENT

The trophic effects of intestinal resection and systemic urogastrone administration on intestinal regeneration were not additive in the present study. While both stimuli independently increased intestinal epithelial cell proliferation and epithelialization compared with control animals, combining the two did not have a positive synergistic effect. Similarly, Goodlad et al[6] found that intestinal resection did not increase the proliferative response of the gut to urogastrone in total parenteral nutrition–fed rats. Intestinal resection enhanced epithelialization to a greater extent than did urogastrone but the effect of urogastrone on epithelialization is dose dependent.[4] In a previous study we found that a higher intravenous dose of urogastrone resulted in epithelialization of 70% of the patched intestinal defect within 7 days, which rate is similar to that achieved with intestinal resection.[4]

The lack of synergism of intestinal resection and urogastrone in promoting epithelialization suggests that these stimuli might have similar mechanisms of action regarding induction of proliferation and epithelial cell migration. The exact mechanism of the adaptive response to intestinal resection remains unclear, but presumably involves a humoral or paracrine stimulant such as enteroglucagon with a trophic effect similar to that of urogastrone. However, Goodlad et al[6] found that plasma enteroglucagon levels were elevated after intestinal resection but did not increase after urogastrone infusion, suggesting that different mechanisms are involved. Both intestinal resection and urogastrone administration are associated with increased DNA and protein synthesis in mucosal cells that may be related to polyamine biosynthesis.[10] Similar increases in ODC activity, the rate-limiting enzyme of polyamine synthesis, occurred with both stimuli. Potentially, the effects of resection might be mediated by modulation of urogastrone receptors on epithelial cells. Receptor binding of urogastrone responds to the concentration of urogastrone and cell density.[11,12] These receptors might be up-regulated earli-

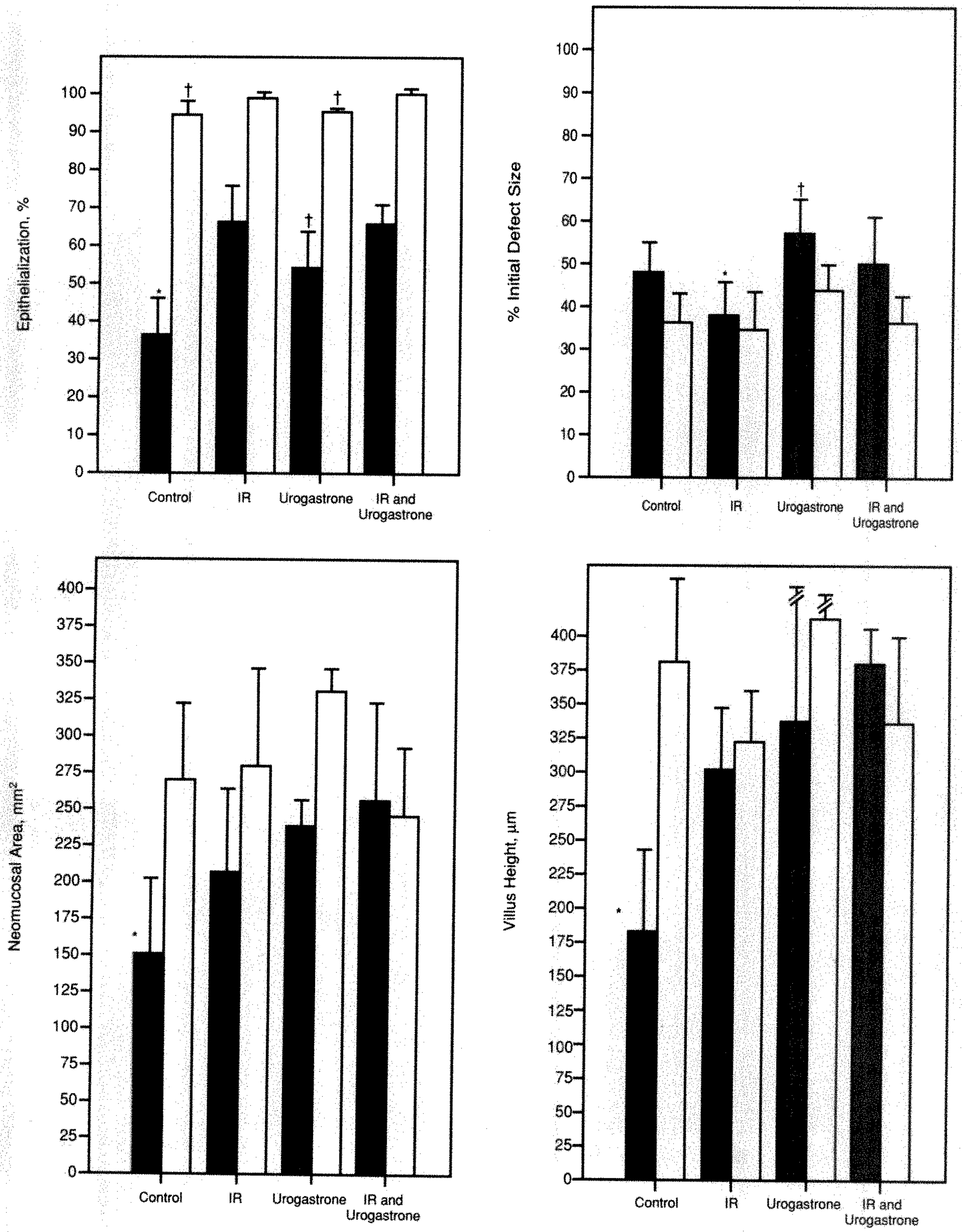

Fig 2.—Comparison of intestinal regeneration. Comparative values at 7 (shaded bars) and 14 (open bars) days are shown. IR indicates intestinal resection. Top left, Epithelialization. Asterisk represents $P<.05$ vs subjects with IR, urogastrone, and IR and urogastrone; and dagger, $P<.05$ vs subjects with IR and IR and urogastrone. Top right, Contraction. Asterisk represents $P<.05$ vs control subjects, those with urogastrone, and IR and urogastrone; dagger, $P<.05$ vs control subjects. Bottom left, Neomucosal area. Asterisk represents $P<.05$ vs subjects with IR, urogastrone, and IR and urogastrone. Bottom right, Villus height. Asterisk represents $P<.05$ vs IR, urogastrone, and IR and urogastrone.

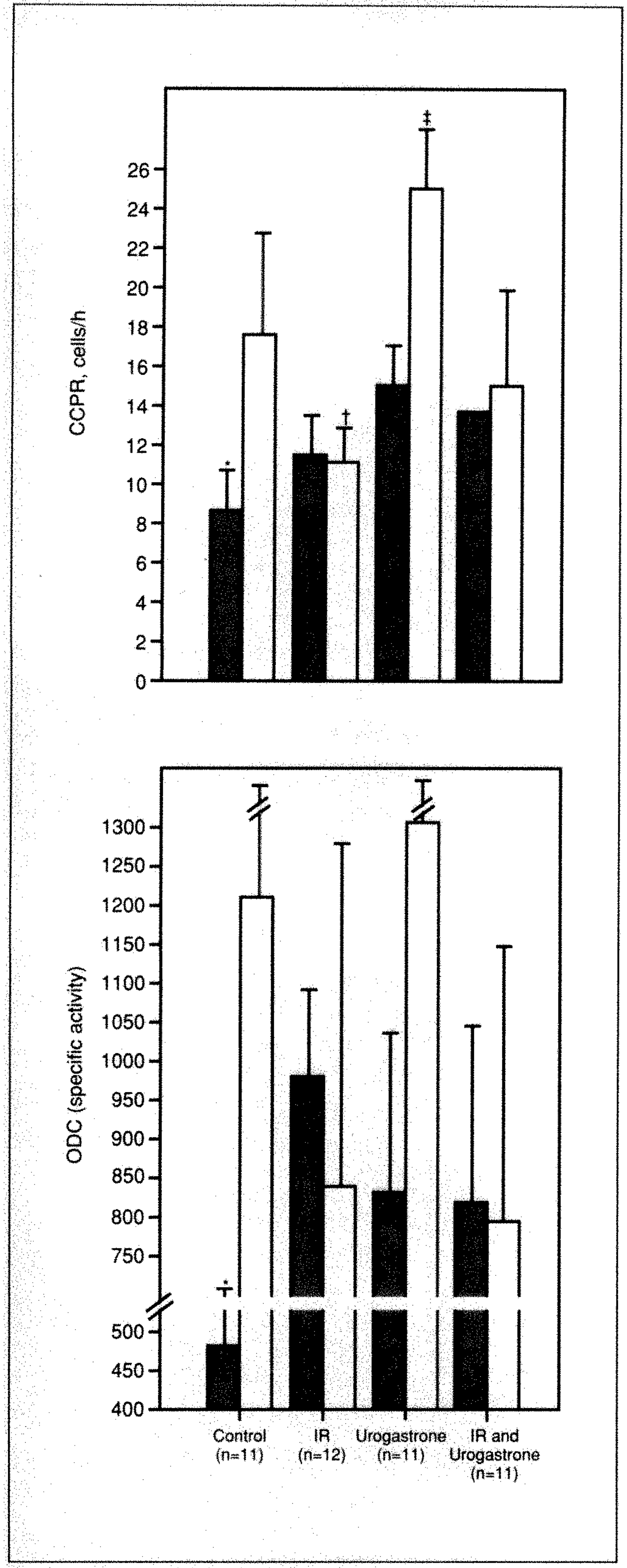

Fig 3.—Comparison of proliferative activity in regenerating mucosa at 7 (shaded bars) and 14 (open bars) days. Comparative values are for crypt cell production rate (CCPR, top) and ornithine decarboxylase activity (ODC, bottom). IR indicates intestinal resection; asterisk, $P<.05$ vs IR, urogastrone, and IR and urogastrone; dagger, $P<.05$ vs control subjects; and double dagger, $P<.05$ vs control subjects, those with IR, and IR and urogastrone.

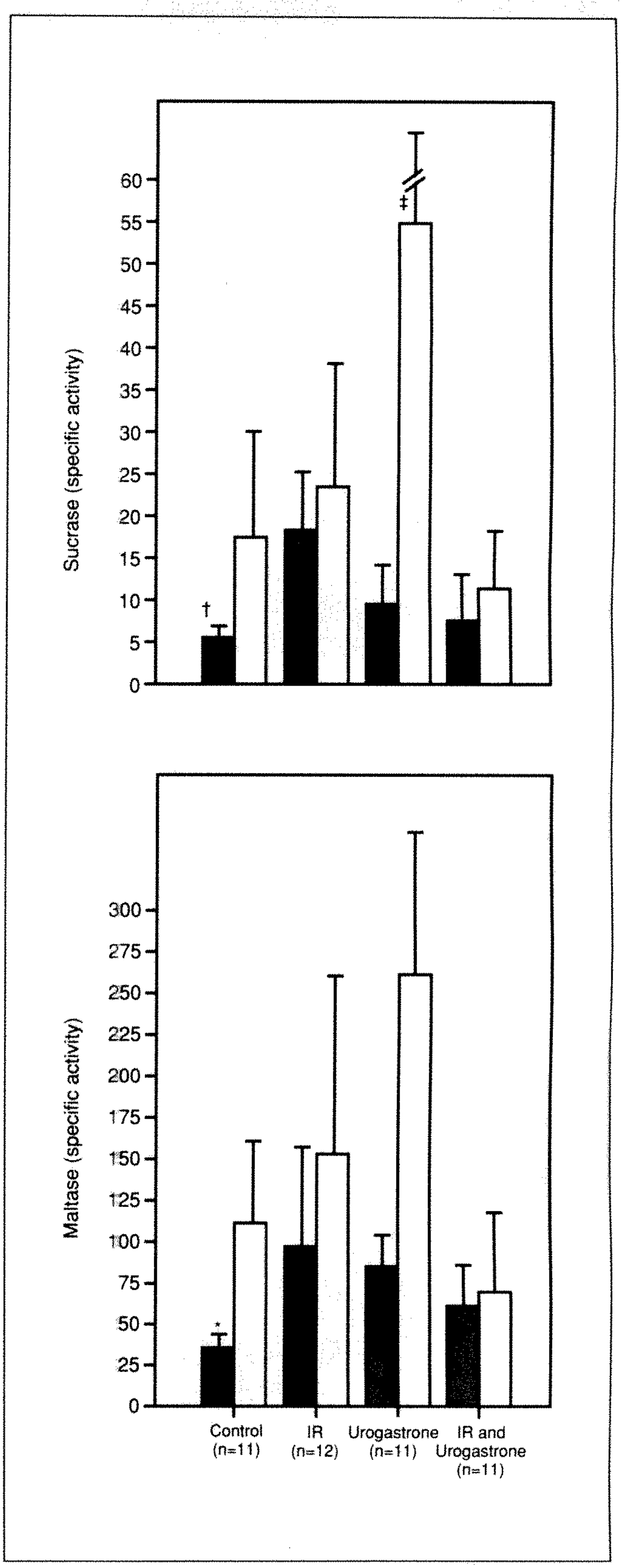

Fig 4.—Comparison of disaccharidase activity in regenerating mucosa at 7 (shaded bars) and 14 (open bars) days. Comparative values are shown for sucrase (top) and maltase (bottom) activity. IR indicates intestinal resection; asterisk, $P<.05$ vs IR and urogastrone; dagger, $P<.05$ vs IR; and double dagger, $P<.05$ vs control subjects and those with IR and urogastrone.

er, thus explaining the early response, but also down-regulated earlier, explaining the decreased response at 14 days and the lack of augmentation when combined with urogastrone. The intestinal nutrient glutamine has a synergistic trophic effect with both intestinal resection and urogastrone, which also suggests a similar mechanism of action.[13] Since both stimuli increase mucosal proliferative activity, perhaps enterocyte nutrients are required to meet the energy demands of further mucosal growth.

The pattern of increase in CCPR during intestinal regeneration is different for intestinal resection and urogastrone. Crypt cell production rate and ODC activity were significantly greater in animals undergoing intestinal resection and/or receiving urogastrone than in control animals 7 days after patching. However, 14 days after patching, CCPR was highest in urogastrone-treated animals and had fallen below that of the control group in the resected animals. Intestinal resection abrogated the effect of urogastrone on CCPR at 14 days. Thus, urogastrone appears to augment the normal pattern of increased proliferative activity, whereas intestinal resection causes a more modest early increase. Furthermore, a previous study suggests that the proliferative response to intestinal resection is more prolonged than with urogastrone.[2]

Since villus height was similar in both urogastrone-treated and resected groups, both stimuli appear to influence epithelial cell migration as well as proliferation. Urogastrone promotes the chemotactic migration of intestinal epithelial cells in vitro.[14] Urogastrone-treated animals had higher disaccharidase activity than resected animals. This suggests that urogastrone has a greater effect on differentiation than intestinal resection.[15]

Consistent with our previous observation, urogastrone inhibited contraction of the patched intestinal defect.[3-5] Intestinal resection, however, caused more rapid contraction and decreased urogastrone's inhibitory effect when these stimuli were combined. Contraction of the patched intestinal defect does not appear to be related to epithelialization, but occurs due to an undefined subepithelial tissue response.[16] Epidermal growth factor stimulates granulation tissue formation.[17] There may be other potential effects, such as the induction on connective tissue cells of growth factor receptors or extracellular matrix receptors necessary for growth factor action. The effect of intestinal resection on contraction after intestinal patching may be mechanical. However, the inhibitory effect of intestinal resection on urogastrone-stimulated proliferative activity may also play a role. Thus, intestinal resection and urogastrone appear to have different effects on subepithelial tissue and consequently on contraction of the patched intestinal defect.

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The urogastrone was supplied by the Chiron Corporation, Emeryville, Calif.

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The Effects of Shear Stress on Endothelial Cell Retention and Function on Expanded Polytetrafluoroethylene

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• We evaluated the adherence of indium 111–radiolabeled endothelial cells to fibronectin-treated expanded polytetrafluoroethylene surfaces exposed to high (437 s^{-1}) vs low (218 s^{-1}) shear and the influence of shear on prostacyclin production. Canine jugular vein factor VIII–positive endothelial cells in passages 3 through 6 were incubated with ^{111}Indium-oxine, and labeled cells were seeded onto fibronectin-treated expanded polytetrafluoroethylene patches. Patches with confluent cells were exposed to shear in a Weissenberg rheogoniometer for intervals ranging up to 60 minutes. Percent endothelial cell retention was determined by gamma counting of patches and media and by histologic evaluation. Prostacyclin production (tritiated radioimmunoassay of 6-keto-prostaglandin $F_{1\alpha}$) was assayed on perfusing media. Results showed no differences in 6-keto-prostaglandin $F_{1\alpha}$ production between shear rates or time periods. Endothelial cell retention did not differ between the shear rates. Rotational shear caused persistent cell loss over time in either high- or low-shear conditions. This persistent cell loss in response to steady rotational shear differs from that in response to identical rates of pulsatile linear shear in our laboratory where cell loss approached zero after 15 minutes.

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The need for improved small-diameter vascular prostheses has led to research of methods to establish an early confluent endothelialized blood-contacting surface. Early methods of endothelial cell transplantation resulted in less than 20% adherence, which then fell to less than 4% at 24 hours after reestablishment of circulation through the implanted grafts.[1] Subsequent studies have shown improved cell adhesion when prosthetic surfaces are pretreated with adhesive proteins, such as fibronectin,[2,3] laminin,[4] or collagen.[5] Retention of seeded endothelial cells by prosthetic surfaces has been studied in vitro following application of pulsatile and steady shears in either linear[6,7] or rotational[8] models. We evaluated, in a rotational-flow device, the adherence of indium 111–radiolabeled endothelial cells to fibronectin-treated expanded polytetrafluoroethylene (ePTFE) surfaces exposed to high and low steady shear rates and the influence of the shear on prostacyclin production.

MATERIALS AND METHODS

Biomaterial Composition

Expanded polytetraflouroethylene (30-µm internodal distance, 0.36-mm thick; WC Gore Co, Flagstaff, Ariz) was used in this study. Circular patches were produced with surface areas measuring 19.6 cm² and with diameters of 5 cm. Before inoculation of the material with endothelial cells, the ePTFE patches were gas-sterilized with ethylene oxide.

Endothelial Cell Harvesting

Endothelial cells were enzymatically harvested from canine external jugular veins with use of our previously published[6] methods of sequential digestion with 0.05% trypsin and 0.05% collagenase and were seeded into 25-cm² culture flasks previously coated with human plasma fibronectin (10 µm/cm²). The cells were maintained in complete media containing M-199 culture medium (GIBCO Biologic Research Laboratories, Grand Island, NY), 10% fetal bovine serum (Hyclone, Logan, Utah), beef lung heparin (5 U/mL; Upjohn, Kalamazoo, Mich), and purified type 1 heparin-binding growth factor (5 ng/mL)). The cells were incubated at 37°C in a humidified 5% carbon dioxide incubator. Culture medium was changed every other day. When confluence was achieved, the cells were trypsinized and split in a 1:3 ratio until an adequate number of cells were obtained for study. At the time of the second passage of cells, an aliquot of suspended cells was stained for factor VIII–related antigen to verify endothelial identity (avidin-biotin immunoperoxidase, Vector Laboratories, Burlingame, Calif). All cells in the study were in passages 3 through 6.

Endothelial Cell Radiolabeling

When an adequate number of cells was obtained, they were enzymatically removed from the culture flask and resuspended in complete medium. Cell counts were performed with a hemocytometer with use of the trypan blue dye exclusion method. ^{111}Indium-oxine (100 µCi/10^6 cells; Syncor, Chicago, Ill) was added to the cells, and the cells were incubated for 30 minutes at room temperature. Complete medium (10 mL) was added to the cells, which were then centrifuged at 1000 rpm for 10 minutes and washed twice more to remove unattached radioactive ^{111}In. The washes were saved and assayed for radioactivity, along with an aliquot of labeled cells to determine labeling efficiency, which averaged 60% in this study. The final cell pellet was reconstituted in sufficient volume of complete medium to cover the ePTFE patches.

Endothelial Cell Seeding

The ePTFE patches were placed in Petri cell culture dishes and coated with 10 µg/cm² of fibronectin. ^{111}In-labeled cells (2×10^5/cm²) were seeded onto the patches and allowed to sit for approximately 20 minutes. Complete medium was then added to the Petri dishes, and the patches were incubated overnight in a 5% carbon dioxide incubator.

Shear Rate/Shear Stress

A Weissenberg rheogoniometer (Model R16/R18, Sangamo Weston Controls Ltd, Sussex, England) was used in this study with a cone-and-plate platen arrangement to shear the endothelial cell–seeded ePTFE patches. The patches were applied to the viscometer platen surfaces with use of an adhesive material (Glue Stick, Faber Castell Distributors, Lewisburg, Tenn). The cone-and-plate platen arrangement, as shown in Fig 1, comprised a 5.0-cm-diameter lower cone with a 2.0° cone angle and a 5.0-cm-diameter upper flat plate. A

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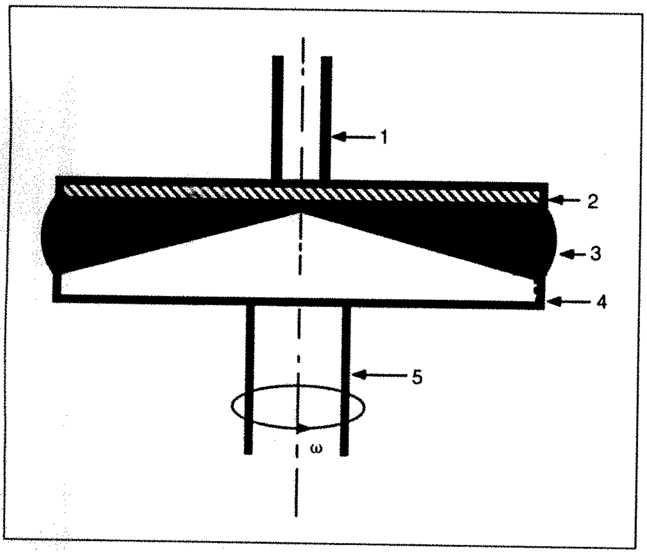

Fig 1.—Cone-and-plate platen arrangement: 1 indicates upper shaft; 2, upper flat plate; 3, conical gap containing the sample; 4, lower (cone) platen; 5, rotating lower shaft; and ω, direction of rotation. From Alkhamis and Beissinger.[12]

perfusate volume of 1.15 mL of M-199 culture medium was contained within the conical gap between the upper and lower platens (Fig 1), with the lower platen made to rotate at a prescribed angular velocity and the upper platen held stationary, while registering a torque signal by the twist of a torsion bar sensed by a displacement transducer. The cone-and-plate geometry is useful at small cone angles when a good approximation to uniform shear is achieved if rotational speed is sufficiently slow.[9,10] Expressions that were used to determine shear rate, shear stress, viscosity, and sample volume are shown in Table 1. The shear rate is equivalent to the velocity gradient in the cone-and-plate geometry, and the shear stress—a tangential force per unit area produced by the fluid in motion on the platen surface resisting its motion—is equivalent to the product of the measured viscosity and the imposed shear rate.

Two levels of shear rate—218 second^{-1} and 437 second^{-1} (corresponding to shear stresses of about 2.5 and 5.0 dyne/cm^2, respectively)—were used in this study. These values approximated the mean shear rates (as determined from Poiseuille's law) of our previous study.[6] In that study, canine external jugular vein endothelial cells were affixed to fibronectin-coated ePTFE tubes. The cells were subjected to pulsatile linear flow at pressures of 120/80 mm Hg and 200/100 mm Hg, which were intended to represent normotensive and hypertensive conditions. At a flow of 100 mL/min, the shear rates were 240 second^{-1} and 520 second^{-1} for the normotensive and hypertensive conditions, respectively.

In the cone-and-plate system, viscosity is used to identify any settling of formed elements during the course of the experiment. This is easily determined, because under the conditions of steady shear, the torque will change if the viscosity changes.

Time Periods to Be Studied

We assessed the effect of shear rate/shear stress on the endothelial cells at five different time periods. Our control time was before the start of the cone-and-plate rotation. After the viscometer was started, it was stopped at the following intervals: 15 seconds, 10 minutes, 30 minutes, and 60 minutes. There were six runs per time interval. After each of these time periods, when the cone and plate stopped rotating, the upper plate was raised and the perfusate was carefully withdrawn from the lower cone with use of a 25-gauge tuberculin syringe. The ePTFE material was then carefully removed from both the lower cone and the upper platen and was fixed immediately in a 1% glutaraldehyde/4% formalin mixture.

Sample Analyses

Once the perfusate was withdrawn from the cone-and-plate viscometer, the following laboratory analyses were performed: (1) The perfusate was frozen at −70°C and later assayed for 6-keto-prostaglandin $F_{1\alpha}$ by tritiated radioimmunoassay techniques (tritiated radioimmunoassay, DuPont/New England Nuclear, North Billerica, Mass). Before freezing, the perfusate was subjected to counting for ^{111}In in a gamma well counter. The radioactivity of the perfusate was expressed as counts per minute per millimeter and was corrected for the decay of the ^{111}In. (2) Before fixation of the ePTFE patches in the glutaraldehyde/formalin mixture, the patches from the upper and lower platens were divided into quarters, placed in labeled tubes containing the glutaraldehyde/formalin mixture, and subjected to counting for radioactivity. The original amount of radioactivity of the ePTFE patch was calculated as the sum of the radioactivity of all the patches and the radioactivity of the perfusate. The retention of endothelial cells was calculated as a percent of the original radioactivity: $C_i = C_g + C_p$ and $EC_r = (C_g/C_i) \times 100\%$, where C_i indicates initial radioactive counts of the ePTFE patch; C_g, radioactive counts of the ePTFE patch following shearing; C_p, radioactive counts of the perfusate after shearing; and EC_r, estimate of the endothelial cell retention. All estimates of the endothelial cell retention and cell loss were corrected for decay of the ^{111}In.

Table 1.—Expressions for the Determination of the Cone-and-Plate Experimental Parameters*

Parameter	Expression
Shear rate (γ)	$\gamma = \Omega/\theta$
Shear stress (σ)	$\sigma = 3T/2\ R^3$
Viscosity (η)	$\eta = \sigma/Y$
Volume (V)	$V = (2/3)\pi R^3 TAN\Theta$

*Ω indicates the angular velocity of the cone (rad/s); Θ, the cone angle (rad); T, the torque (G − cm^2/s^2); and R, the radius of the cone and/or plate.

After counting for radioactivity of the patches, half the samples from each group were evaluated by scanning electron microscopy. The remaining sections were stained with Gill's hematoxylin, and estimates of cell confluence were determined. Three "blinded" observers viewed the patches under the light microscope to determine the cell density, which was graded as follows: 4+, confluent; 3+, nearly confluent; 2+, nonconfluent; and 1+, scattered cells.

Light Microscopy

Following fixation of all the patches in the 1% glutaraldehyde/4% formalin mixture, half the patches were stained with hematoxylin-eosin and examined under the light microscope for estimates of cell confluence and for histologic analysis.

Scanning Electron Microscopy

All specimens were examined under the scanning electron microscope with the use of previously described standard techniques.[11] Patches were stained with tannic acid–osmium–thiocarbohydrazide–osmium and dehydrated in graded alcohols. The patches were critical-point dried, carbon and palladium evaporated, and viewed with a scanning electron microscope (JEOL JSM-35, JEOL USA, Inc, Electron Optics Division, Peabody, Mass).

Data Analysis

The data from all the groups were subjected to a multivariate analysis of variance for detection of differences between groups, with a modified *t* test to detect differences within the groups. $P < .05$ was considered statistically significant.

RESULTS

No significant differences in prostacyclin production were noted between low and high shear and between the different time periods (Fig 2 and Table 2), nor were differences detected in endothelial cell retention between low and high shear at any time point (Fig 3 and Table 3). However, shear results obtained in the rotational viscometer showed persistent cell loss over time. At low shear, mean (±SD) endothelial cell retention at 30 minutes and 60 minutes (71.4% ± 8.6% and 59.5% ± 6.3%, respectively) was significantly decreased from control values (92.0% ± 3.8%) ($P < .02$). At high shear, endothelial cell retention at 30 minutes and 60 minutes

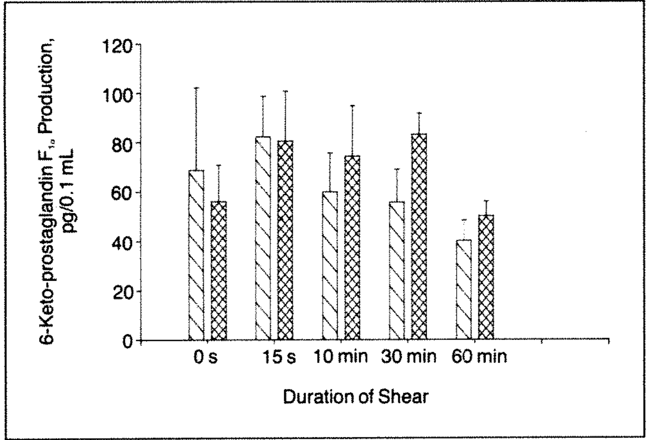

Fig 2.—6-Keto-prostaglandin $F_{1\alpha}$ production in expanded polytetrafluoroethylene patches as a function of time and shear rate. Hatched bars indicate low shear; cross-hatched bars, high shear.

Table 2.—6-Keto-Prostaglandin $F_{1\alpha}$ Production*

	0 s	15 s	10 min	30 min	60 min
Low shear	68.7±66.9	82.2±36.8	60.0±35.1	55.8±29.6	40.2±18.5
High shear	56.1±29.4	80.5±40.4	74.4±45.6	83.2±19.2	50.2±13.2

*Data are mean±SD.

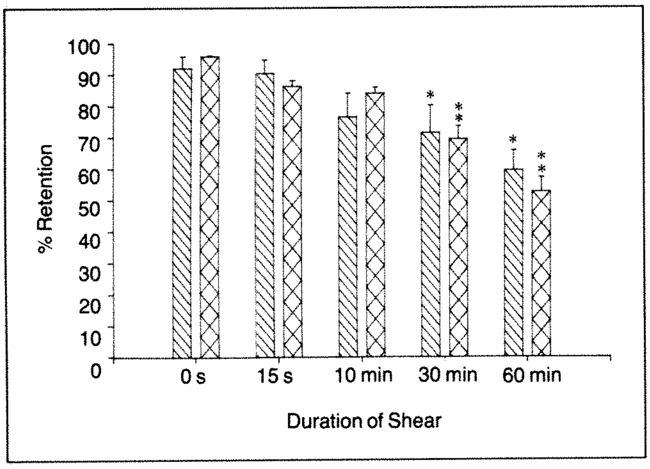

Fig 3.—Percent endothelial cell retention by expanded polytetrafluoroethylene surfaces following exposure to high vs low shear rate. Cell retention was calculated as follows: radioactive counts per minute of the graft after shear exposure divided by the initial counts per minute of the graft times 100%. Single asterisk indicates significant difference from 0 seconds ($P<.02$); double asterisk, significant difference from 0 and 15 seconds and 10 minutes ($P<.001$). Hatched bars indicate low shear; cross-hatched bars, high shear.

Table 3.—Endothelial Cell Retention

	0 s	15 s	10 min	30 min	60 min
Low shear	92.0±7.7	90.3±9.7	76.4±16.8	71.4±19.3	59.5±14.1†
High shear	95.8±0.5	86.1±3.6	83.9±4.2	69.4±9.2	52.7±10.2‡

*Data are mean±SD.

†Significant difference ($P<.05$) vs 0 seconds, 15 seconds, and 10 minutes.

‡Significant difference ($P<.05$) vs 0 seconds, 15 seconds, 10 minutes, and 30 minutes.

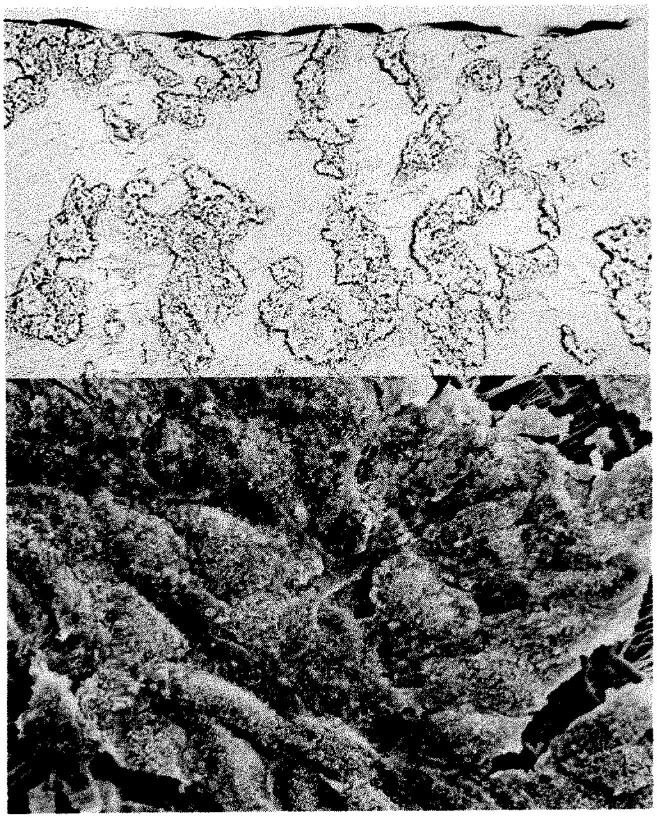

Fig 4.—Top, Photomicrograph of expanded polytetrafluoroethylene (ePTFE) surface following a 60-minute exposure to high shear shows a confluent layer of endothelial cells covering the ePTFE (hematoxylin-eosin, original magnification ×650). Bottom, Scanning electron micrograph of ePTFE surface following a 60-minute exposure to high shear shows a confluent area of endothelial cells. The line between the sheet of endothelial cells is likely an artifact (original magnification ×1100).

(69.4%±4.1% and 52.7%±4.6%, respectively) was significantly decreased compared with control values, and 15-second and 10-minute values (95.8%±0.3%, 86.1%±1.8%, 83.9%±1.9%, respectively; $P<.001$). Cell retention at any given time point did not differ between high and low shear. Semiquantitative grading of the degree of confluence showed a consistent trend with the radioactivity determinations of cell retention.

Light microscopy and scanning electron microscopy showed degrees of cell retention consistent with the above results. Figure 4 shows the near confluent cell layer following exposure to 60 minutes of high shear, while Fig 5 shows the similar surface remaining following 60 minutes of exposure to low shear. These histologic analyses show areas of cell denudation, suggesting that cells are shed primarily in clusters rather than individually.

COMMENT

These results demonstrate a persistent loss of seeded endothelial cells from the fibronectin-treated ePTFE surfaces as a function of time at a rate not approaching an asymptote. There appears to be no significant difference in the rate of cell loss under high vs low shear conditions at the shear rates studied. Longer-term studies may provide insight into the duration of persistent cell loss and possible recovery of cell numbers through the process of endothelial cell proliferation. However, the results reported herein proved disappointing for the clinical strategy of endothelial cell seeding.

In our study, shear was determined on the basis of relatively high and low physiologic levels of shear rate. In a recent study[12] concerning the effect of artificial surfaces on red blood

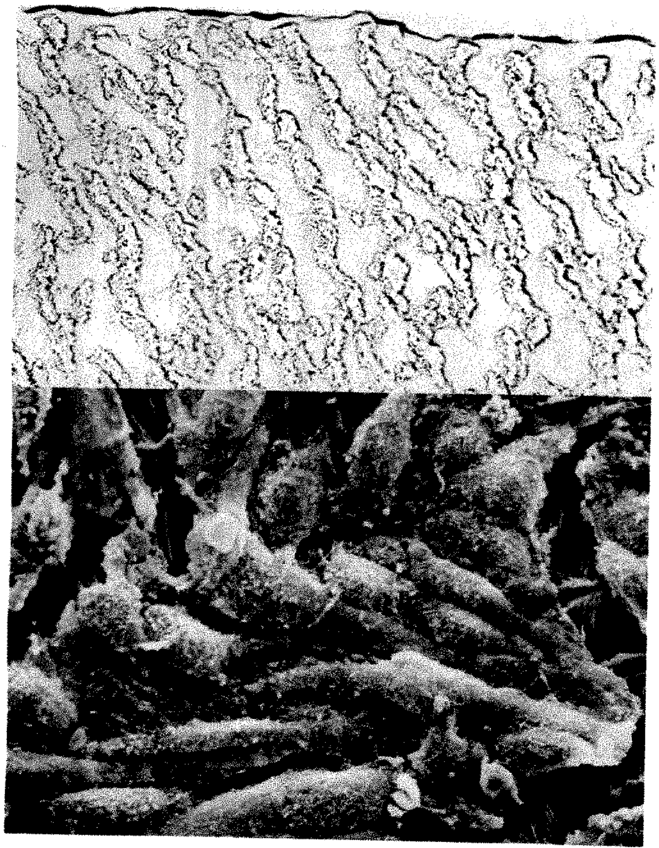

Fig 5.—Top, Photomicrograph of expanded polytetrafluoroethylene (ePTFE) surface following a 60-minute exposure to low shear shows a confluent layer of endothelial cells covering the ePTFE (hematoxylin-eosin, original magnification ×650). Bottom, Scanning electron micrograph of ePTFE surface following a 60-minute exposure to low shear shows a confluent area of endothelial cells. The line between the sheet of endothelial cells is likely an artifact (original magnification ×1100).

cells and platelets, single platelet reduction, ie, the loss of platelets due to aggregation and adhesion, correlated with shear rate rather than with shear stress.

Fibronectin is an adhesive protein found in the basement membrane and contains the arginine-glycine-aspartic acid (RGD) sequence, which promotes endothelial cell receptor binding. As such, it is a logical choice for use in the promotion of endothelial cell adhesion. Many factors may explain the lack of resistance to desquamation following exposure to shear stress. Past studies from our group[7] have shown that canine jugular vein endothelial cells subjected to linear pulsatile flow through a pulse-duplicating apparatus are resistant to desquamation from fibronectin-treated ePTFE surfaces. However, the surface area–to-volume ratios of these two systems were dissimilar. In the present study, the surface area–to-volume ratio was 3.4 times larger than that in our previous study.[6,7] The surface area–to-volume ratio can become important at low shears. An examination of the potential for blood hemolysis in a rotational viscometer system demonstrated that interaction between the blood and the solid interface was important in determining the amount of hemolysis.[13] The surface–perfusing media interaction may be important in determining surface effects of the perfusing media on the endothelial cells. It is thus critical to evaluate the role of steady shear obtained in a rotational viscometer vs linear pulsatile shear in promoting cell desquamation. The results in our present study also differ from those reported previously by Pratt et al,[8] who used a similar cone-and-plate viscometer system. However, their studies were performed on other matrices than ePTFE. Another possible explanation for the greater resistance to desquamation seen in the pulsatile flow model is a cytoskeletal reorganization in response to pulsatility, leading to increased cell adhesiveness.

The lack of difference in endothelial cell production of prostacyclin under high vs low shear was surprising. In related studies evaluating the effect of shear on endothelial cell prostacyclin production, when cells were seeded onto Hytrel patches (Dupont, Wilmington, Del), we demonstrated a significant increase in prostacyclin production at 15 seconds under the high-shear condition compared with the low-shear condition. Moreover, the amount of prostacyclin in the perfusate increased over time, showing a cumulative effect consistent with observations by Frangos et al.[14] These differences may in part reflect the use of ePTFE as a matrix. Furthermore, the magnitudes of shear in the high-shear conditions used by Frangos et al were greater than those used in our current study. Thus, the prosthetic material used clearly exerts a major effect on endothelial cell function following seeding onto fibronectin-treated surfaces.

For endothelial cell seeding to be a clinically effective tool, we need to optimize the adhesion and retention of endothelial cells by the surface, but we also need to optimize the microenvironment onto which the endothelial cell is seeded to optimize the cell's function. The application of a single basement membrane–adhesive protein to a highly artificial matrix in the hope of promoting endothelial cell retention and optimizing its function is in need of further evaluation. It is likely that more complex environments must be created for the endothelial cell to promote its retention and antithrombotic activities and not activate the cell to release substances that may lead to long-term pseudointimal hyperplastic lesions.

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Clinical Note

Surgical Aspects of Sclerosing Encapsulating Peritonitis

Dilip S. Kittur, MD, ScD; Subhash W. Korpe, MD; Roman E. Raytch, MD; Gardner W Smith, MD

• Sclerosing encapsulating peritonitis (SEP) is associated with the administration of beta-blocking agents as well as continuous ambulatory peritoneal dialysis. The predisposing factors in the latter group are recurrent peritonitis, presence of acetate in the dialysate, and antiseptics used during bag exchanges. We report a case of SEP following chronic ambulatory peritoneal dialysis and review the literature on this benign yet potentially lethal condition. Sclerosing encapsulating peritonitis frequently leads to intestinal obstruction, small-bowel necrosis, enterocutaneous fistulas, and malnutrition. There is a high incidence of anastomotic failure when a resection and primary intestinal anastomosis is performed in patients with SEP. Although SEP is not commonly reported in the surgical literature, its importance to surgeons is indicated by the fact that the overall mortality rate is close to 60% in patients with SEP who develop surgical complications.

(*Arch Surg.* 1990;125:1626-1628)

Sclerosing encapsulating peritonitis (SEP) is an infrequent but lethal complication of peritoneal dialysis[1] and of the administration of β-adrenergic blocking agents.[2-6] Since the original description of this entity,[7,8] sporadic reports of SEP have appeared in medical and nephrology journals.[3,6,9-12] However, the lethality of this disease is related to surgical problems encountered in these patients, such as intestinal obstruction, intestinal necrosis, and enterocutaneous fistulas. Despite a 60% mortality rate associated with the surgical complications of SEP,[1] there is a paucity of articles regarding SEP in the surgical literature.

This report describes a patient with chronic renal failure who had SEP as a consequence of chronic ambulatory peritoneal dialysis (CAPD). The SEP eventually progressed to subacute and then acute small-bowel obstruction, leading to massive intestinal necrosis. In the context of this case, we review the literature pertinent to the surgical problems caused by SEP, since these problems have not been widely appreciated by surgeons. The patient's protracted course and numerous complications indicate that SEP is more of a surgical entity than is currently recognized. This review provides a balanced perspective on the etiology, pathology, clinical presentation, and management of this dire complication of peritoneal dialysis and treatment with beta-blockers.

REPORT OF A CASE

A 41-year-old black man developed chronic renal failure in 1973 and underwent hemodialysis for 9 years. In March 1982, a Tenchehoff catheter was placed, and CAPD was started. During CAPD, the patient did not develop bacterial or fungal peritonitis. However, after 29 months of CAPD, a *Pseudomonas aeruginosa* infection developed at the exit site of the dialysis catheter. This necessitated removal of the catheter and resumption of hemodialysis. Two subsequent attempts to place a catheter for CAPD failed because of numerous adhesions between the abdominal viscera and the parietal peritoneum

Approximately 3 years after CAPD was discontinued, the patient developed abdominal pain, intermittent diarrhea, and constipation. Results of contrast studies of the upper gastrointestinal tract were unremarkable except for a questionable antral ulcer. Six months later he was hospitalized for partial small-bowel obstruction. By this time he had overt malnutrition. Results of physical examination were remarkable for a palpable mass in the central portion of the abdomen. Plain films of the abdomen showed dilated small-bowel loops and air fluid levels. A subsequent small-bowel series demonstrated distention of the stomach, duodenum, and jejunum as well as numerous local dilatations of the small bowel. There were also areas of localized thickening consistent with inflammatory changes in the bowel wall (Fig 1). The patient was treated nonoperatively until his presentation to the emergency department 4 months later with the clinical and radiologic picture of acute small-bowel obstruction (Fig 2). Exploratory laparotomy revealed that the whole small intestine was encased in a thick and fibrous peritoneal capsule characteristic of SEP. Adhesions were lysed, and 2.4 m of clearly gangrenous small bowel had to be resected with a primary anastomosis to restore intestinal continuity. Pathologic examination of the resected specimen showed a markedly thickened and fibrous serosa, with areas of ischemia, as well as necrosis of mucosa, submucosa, and muscularis. On the seventh day after surgery, the patient developed an anastomotic leak, leading to peritonitis and multiple intra-abdominal abscesses. He underwent exploratory surgery again, and the bowel was diverted by constructing an enterocutaneous fistula proximally and an ileostomy distally, while the abscesses were drained.

Postoperatively, the patient received total parenteral nutrition until the inflammation was resolved and healing was complete. After 8 months an attempt was made to close the ileostomy; this failed due to anastomotic dehiscence. Accordingly, another ileostomy was created, but the patient eventually died of sepsis.

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Reprint requests to Francis Scott Key Medical Center, 4940 Eastern Ave, Baltimore, MD 21224 (Dr Kittur).

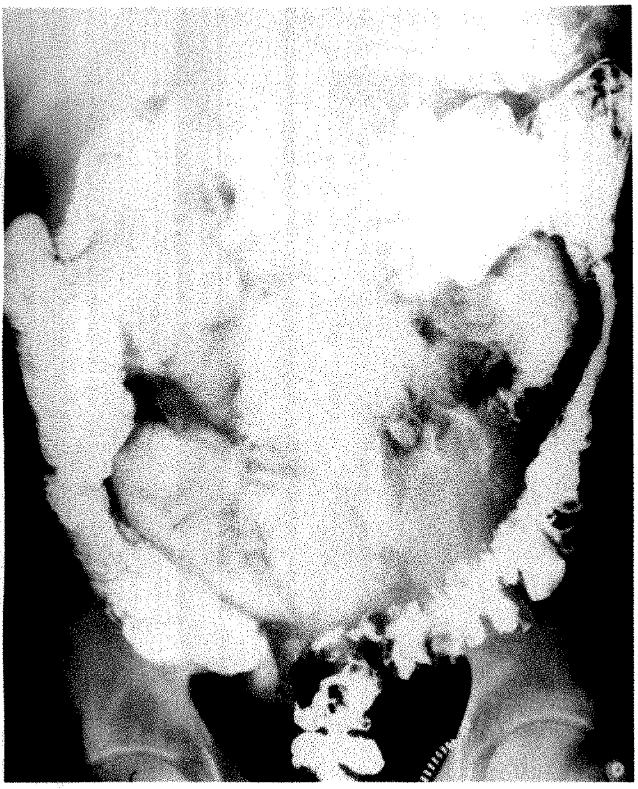

Fig 1.—Small-bowel series taken 2 months prior to the patient's presentation with acute small-bowel obstruction. The examination reveals multiple areas of dilatation and narrowing in the small intestine and delayed emptying of the contrast material.

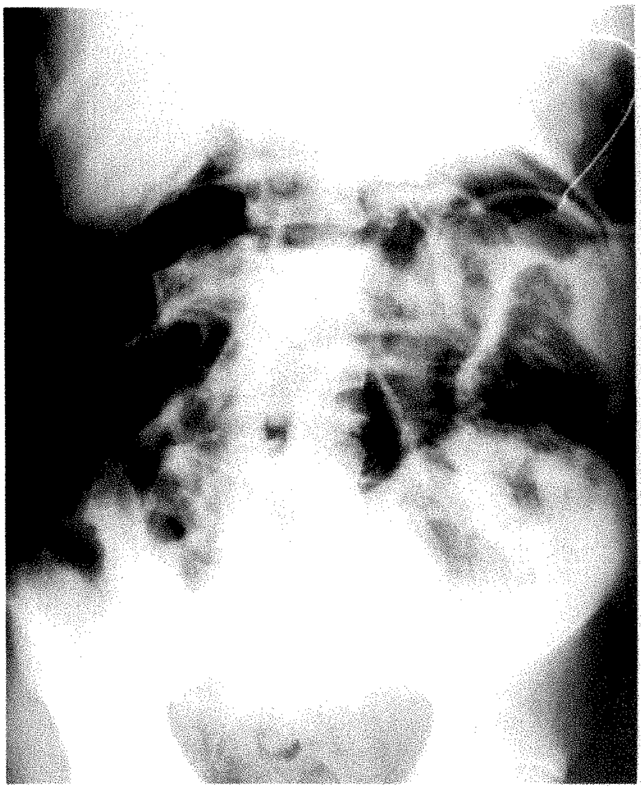

Fig 2.—Plain film of the abdomen at the time of the patient's presentation to the hospital with acute complete small-bowel obstruction. Note the complete absence of gas in the colon and rectum.

COMMENT

Sclerosing encapsulating peritonitis occurring as a complication of CAPD is clinically characterized by a relentless progression from nausea, vomiting, abdominal pain, and impaired ultrafiltration during CAPD to complete small-bowel obstruction, necessitating surgical intervention. Pathologically, SEP appears to be an inflammatory process that transforms the peritoneal membrane into thick fibrous tissue due to fibroconnective tissue proliferation. The fibrous tissue eventually replaces the normal mesothelial lining of both the visceral and parietal layers of the peritoneum. Although this is a histologically benign process, its clinical significance is indicated by a reported mortality rate of 60% within 4 months of diagnosis.[1] In this context, it is remarkable that our patient was alive 14 months after the diagnosis of this lethal complication. The possible factors pertinent to his survival are discussed below.

In an international registry of 68 patients, Slingeneyer[1] has identified four factors in the development of SEP among patients undergoing CAPD: (1) recurrent peritonitis, (2) the presence of acetate in the dialysate, (3) antiseptics used during bag exchanges, and, possibly, (4) the concomitant oral administration of beta-blocking agents. In view of these risk factors, the most plausible pathophysiologic event in the development of SEP appears to be an inflammatory process initiated by peritonitis and peritoneal exposure to antibiotics. This inflammatory response would then progress to the development of serosal fibrosis, leading to SEP.[12] The most popular hypothesis appears to be recurrent episodes of peritonitis as a causative factor.[9] Novello and Port,[13] elaborating on this thesis, postulate that various bacteria release endotoxins that stimulate monocytes to produce interleukin 1, which in turn causes fibroblasts to proliferate and deposit collagen. Acetate in the dialysate may act similarly, by causing an inflammatory response of the peritoneum.[14,15] Various antiseptics, such as formaldehyde, chlorhexidine,[16] and sodium hypochloride,[17-19] have been thought to incite SEP, probably by a similar mechanism. An interesting feature of our case is that, to our knowledge, our patient was never exposed to any of the above-mentioned risk factors. He also did not take any of the beta-blockers,[2] such as practolol,[3,4] propranolol,[5] metoprolol, and atenolol,[6] that have been implicated in the development of SEP.

The absence of previously reported etiologic agents in our patient leads us to conclude that the mere presence of the silicone catheter in the peritoneal cavity was sufficient to evoke an intense fibrotic reaction. Others have implicated the silicone catheter itself in the pathogenesis of SEP.[20-22] Another possibility is the hypersensitivity of certain individuals to mild peritoneal stimulation, bringing about an exaggerated interleukin 1 response, with consequent deposition of excessive amounts of collagen and fibrous tissue. The normal healing of bowel anastomoses may well be hampered by this peritoneal thickening, resulting in an increased incidence of anastomotic leaks and enterocutaneous fistulas.

The most common complications of SEP appear to be intestinal obstruction, small-bowel necrosis, enterocutaneous fistulas, and malnutrition. Our patient presented to the surgical service with acute small-bowel obstruction and subsequently manifested the entire gamut of these complications. In addition to the fibrous and thickened peritoneum encapsulating the small bowel, he had necrosis of about 2.4 m of intestine. Intestinal anastomoses failed to heal on two separate occasions. This suggests that, when patients with SEP need intestinal resection, primary anastomosis may be unwise, and complications may be avoided by construction of an enterostomy. The malnutrition that is common in these patients may further delay intestinal healing and should be treated aggressively. Given our early success in treating this patient with long-term home hyperalimentation, we fully agree with Pusateri et al[12] that long-term home parenteral hyperalimentation forms an integral part of the management of SEP and its complications. We further believe that, at least in some cases, an aggressive surgical approach to this complication may be more hazardous than long-term nutritional management. Clearly, however, necrotic intestine must be resected.

The surgical complications of SEP are potentially lethal. In general, a nonaggressive surgical approach may be beneficial in these patients, considering the poor healing capability of intestinal anastomoses. If laparotomy and resection of gangrenous bowel is necessary, enterostomies may be preferable to primary anastomoses. Finally, the value of total parenteral nutrition in these patients cannot be overemphasized.

Dr Korpe acknowledges the assistance of R. D. Birla Smarak Kosh, of Bombay, India. We thank Pamela Morris for secretarial assistance in preparing the manuscript.

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In Other AMA Journals

Apolipoproteins A-I and B as Predictors of Angiographically Defined Coronary Artery Disease

Richard A. Reinhart, MD; Kosasih Gani, MD; Michael R. Arndt, MT; Steven K. Broste, MS

Apolipoprotein A-I and B concentrations were measured in 502 patients undergoing diagnostic cardiac catheterization to assess the predictive power of apolipoproteins B and A-I to discriminate between patients with coronary artery disease and those with normal coronary arteries as defined by coronary arteriography. The strength of the associations was compared with that of the associations between traditional risk factors (eg, smoking status, cholesterol levels) and coronary artery disease. The study population consisted of 154 women (mean age, 62.9 years) and 348 men (mean age, 59.6 years). The apolipoprotein A-I concentration averaged (±SD) 124±25 mg/dL and the apolipoprotein B concentration, 98±24 mg/dL. In all cases, the apolipoprotein measures showed a larger univariate difference between the "normal" (no coronary artery disease) group (66 patients) and the group with coronary artery disease (436 patients) than did the corresponding standard lipoprotein measures. The variable with the strongest association with coronary artery disease was the ratio of apolipoprotein A-I to apolipoprotein B, followed by apolipoprotein B level. These findings were confirmed using logistic regression, adjusting for other coronary artery disease risk factors. Fasting status did not affect apolipoprotein A-I or B concentrations. We conclude that the use of apolipoprotein A-I and B concentrations gives additional information to that supplied by lipoprotein measures to help predict the presence of coronary artery disease. Since traditional lipid measures may be changed by a meal, apolipoproteins A-I and B might be more useful measures when the fasting status of a patient is in question (*Arch Intern Med.* 1990;150:1629-1633).

Reprint requests to Marshfield Clinic, 1000 N Oak Ave, Marshfield, WI 54449 (Dr Reinhart).

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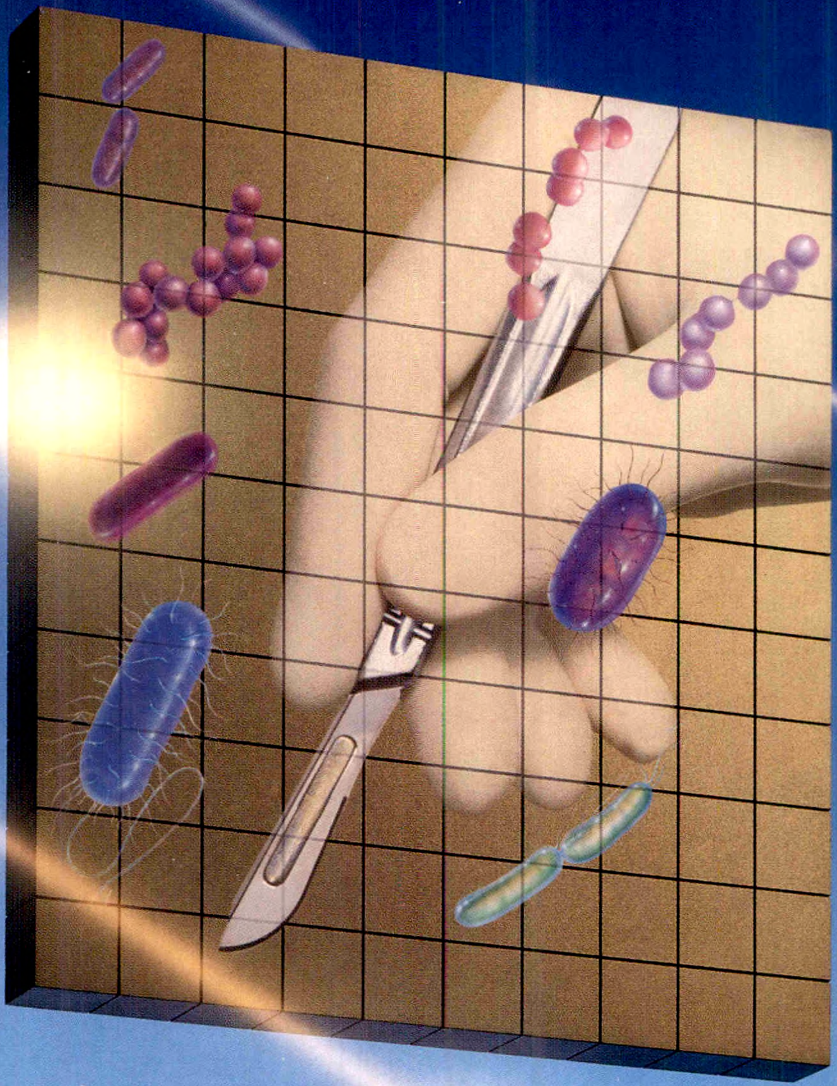

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

TIMENTIN® **sterile ticarcillin disodium and clavulanate potassium** for Intravenous Administration

INDICATIONS AND USAGE: TIMENTIN[1] is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Bacterial Septicemia: including bacteremia, caused by ß-lactamase producing strains of *Klebsiella* spp., *E. coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* (and other *Pseudomonas* species). Lower Respiratory Infections: caused by ß-lactamase producing strains of *Staphylococcus aureus*, *Hemophilus influenzae* and *Klebsiella* spp. Bone and Joint Infections: caused by ß-lactamase producing strains of *Staphylococcus aureus*. Skin and Skin Structure Infections: caused by ß-lactamase producing strains of *Staphylococcus aureus*, *Klebsiella* spp., and *E. coli*. Urinary Tract Infections (complicated and uncomplicated): caused by ß-lactamase producing strains of *E. coli*, *Klebsiella* spp., *Pseudomonas aeruginosa* (and other *Pseudomonas* species), *Citrobacter* spp., *Enterobacter cloacae*, *Serratia marcescens*, and *Staphylococcus aureus*. Gynecologic Infections: Endometritis caused by ß-lactamase producing strains of *B. melaninogenicus*; *Enterobacter* spp. (including *E. cloacae**), *Escherichia coli*, *Klebsiella pneumoniae*,* *Staphylococcus aureus*, and *Staphylococcus epidermidis*.

While TIMENTIN is indicated only for the conditions listed above, infections caused by ticarcillin susceptible organisms are also amenable to TIMENTIN treatment due to its ticarcillin content. Therefore, mixed infections caused by ticarcillin susceptible organisms and ß-lactamase producing organisms susceptible to TIMENTIN should not require the addition of another antibiotic.

ADVERSE REACTIONS: As with other penicillins, the following adverse reactions may occur: *Hypersensitivity reactions:* skin rash, pruritus, urticaria, arthralgia, myalgia, drug fever, chills, chest discomfort, and anaphylactic reactions. *Central nervous system:* headache, giddiness, neuromuscular hyperirritability or convulsive seizures. *Gastrointestinal disturbances:* disturbances of taste and smell, stomatitis, flatulence, nausea, vomiting and diarrhea, epigastric pain. *Hemic and Lymphatic systems:* thrombocytopenia, leukopenia, neutropenia, eosinophilia and reduction of hemoglobin or hematocrit. Prolongation of prothrombin time and bleeding time. *Abnormalities of hepatic and renal function tests:* elevation of serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), serum alkaline phosphatase, serum LDH, serum bilirubin. Rarely, transient hepatitis and cholestatic jaundice–as with some other penicillins and some cephalosporins. Elevation of serum creatinine and/or BUN, hypernatremia. Reduction in serum potassium and uric acid. *Local reactions:* pain, burning, swelling and induration at the injection site and thrombophlebitis with intravenous administration. *Overdosage:* As with other penicillins, TIMENTIN in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures. Ticarcillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding and pharmacokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by hemodialysis.

CONTRAINDICATIONS: TIMENTIN is contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH TIMENTIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER DRUGS. IF AN ALLERGIC REACTION OCCURS, TIMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE PROVIDED AS INDICATED.**

PRECAUTIONS: While TIMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, organ system functions should be assessed periodically during therapy.

Bleeding manifestations have occurred in some patients receiving ß-lactam antibiotics. These reactions have been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal impairment. If bleeding manifestations appear, TIMENTIN treatment should be discontinued and appropriate therapy instituted.

TIMENTIN has only rarely been reported to cause hypokalemia. Periodic monitoring of serum potassium may be advisable in patients receiving prolonged therapy.

Pregnancy (Category B): Reproduction studies have been performed in rats given doses up to 1050 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to TIMENTIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

DOSAGE AND ADMINISTRATION: TIMENTIN should be administered by intravenous infusion (30 min.). Usual recommended dose for systemic and urinary tract infections for average (60 kg) adults is 3.1 Gm TIMENTIN (3.1 Gm vial containing 3 Gm ticarcillin and 100 mg clavulanic acid) given every 4 to 6 hours. For gynecologic infections TIMENTIN should be administered as follows: Moderate infections 200 mg/kg/day in divided doses every 6 hours and for severe infections 300 mg/kg/day, based on ticarcillin content, in divided doses every 4 hours. For patients weighing less than 60 kg, the recommended dosage is 200-300 mg/kg/day, based on ticarcillin content, given in divided doses every 4 to 6 hours. In urinary tract infections, a dosage of 3.2 Gm TIMENTIN (3.2 Gm vial containing 3 Gm ticarcillin and 200 mg clavulanic acid) given every 8 hours is adequate. Please see official package insert for details on dosages for other patients, including those with renal insufficiency, and directions for use.

SUPPLIED: 3.1 Gm and 3.2 Gm Standard Vials; 3.1 Gm and 3.2 Gm Piggyback Bottles; 31 Gm Bulk Pharmacy Package; 3.1 Gm ADD-Vantage™ Antibiotic Vial.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections. 7548/H-BS ©1990, Beecham Laboratories

Reference:

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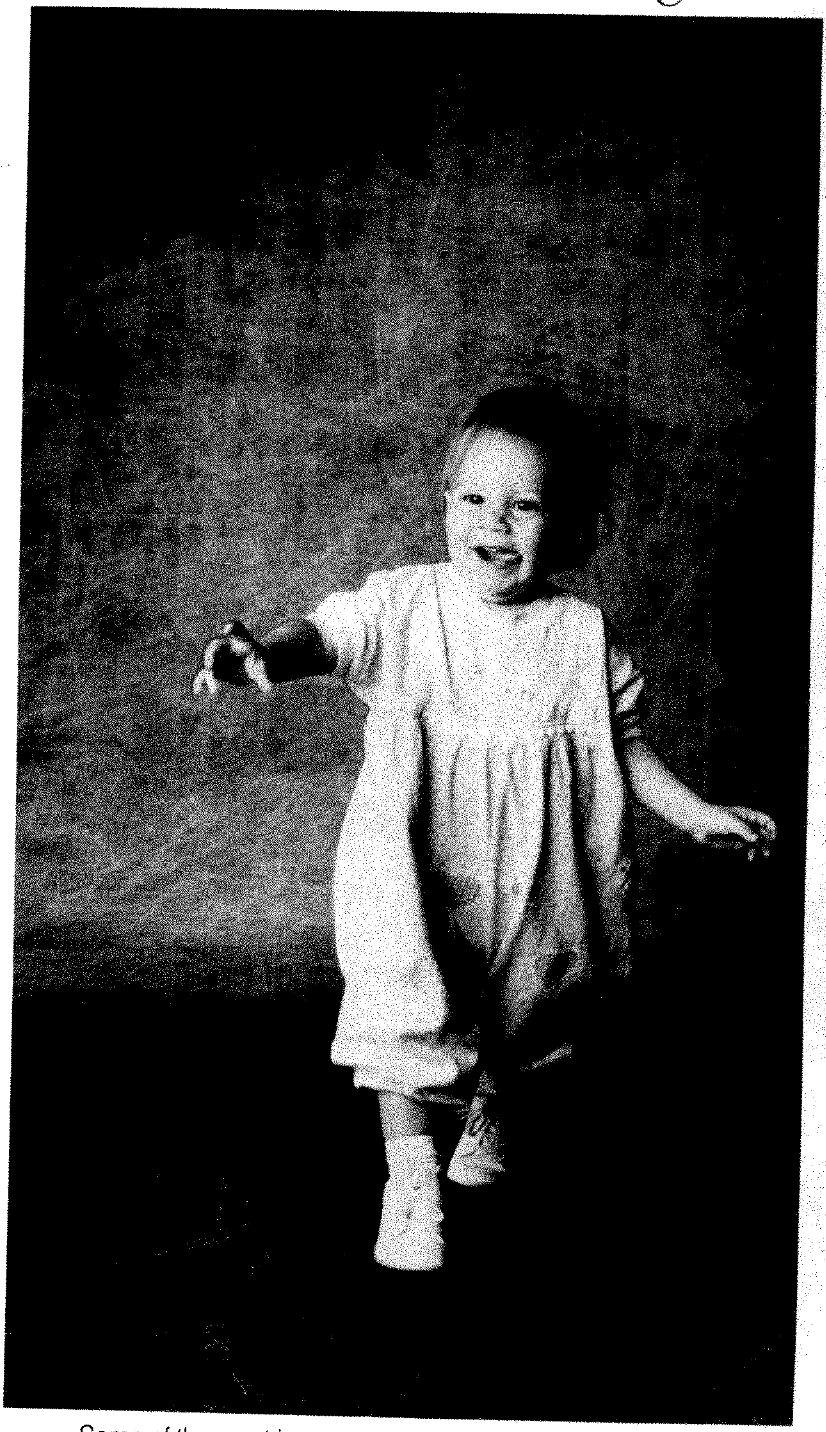

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Correspondence and Brief Communications

Resident Training

To the Editor.—In the April 1990 issue of the ARCHIVES, Doerr et al[1] reviewed a 10-year experience with pancreaticoduodenectomy at four teaching hospitals of the State University of New York, Buffalo. There were 61 cases, an average of six per year and 1.5 per hospital per year. Fifty-five residents performed one pancreaticoduodenectomy during their training; three residents did two such procedures. Operative morbidity and mortality were an acceptable 36% and 8%, respectively. The authors conclude that these results justify preserving pancreaticoduodenectomy as an important part of surgical training. Training for what? Such limited experience hardly connotes expertise; it arguably fails to impart even competence. Furthermore, as noted by Barnes[2] in the same issue, 60% to 75% of present general surgical graduates go on to other fields (eg, cardiothoracic surgery and plastic surgery). Few of the latter are likely to perform complex pancreatic surgery again, yet they receive the same experience as those who are planning a career in general surgery and will need skills in this area. Doerr et al seem to believe that because operations such as pancreaticoduodenectomy are technically demanding, and safely performed by residents, they represent valuable teaching tools to be used by all, regardless of career choice. However, the same could be said for coronary bypass, kidney transplantation, major vascular reconstruction, and cleft lip/palate repair, which are also technically demanding and more commonly performed than pancreaticoduodenectomy. If the goal of general surgical training is merely to impart all-purpose technical proficiency, it would be more productive to use cases of the latter type for such teaching, rather than rare operations like Whipple's operation. This would return surgical education to what it once was, and produce true "general" surgeons.

NATHAN W. PEARLMAN, MD
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1. Doerr RJ, Yildiz I, Flint LM. Pancreaticoduodenectomy: university experience and resident education. *Arch Surg.* 1990;125:463-465.
2. Barnes RW. The next generation of surgical residencies: what are the challenges and the opportunities? *Arch Surg.* 1990;125:433-436.

In Reply.—The article that Drs Pearlman, Norton, and Stiegmann refer to included the clinical results of radical pancreaticoduodenectomy within the context of a surgery resident education program, as well as observations regarding the educational value of this complex and demanding operation.

The purpose of complex surgical experience during residency is to provide a demanding exercise in the integration of knowledge, technical skill, and judgment in a patient care situation in which the stakes are high but the environment is controlled by an experienced faculty supervisor so that maximum patient safety is achieved. In our article we sought to support this conceptual approach to one operation, radical pancreaticoduodenectomy. We hoped to provide evidence that the resident training environment provides consistent pressure for improved results through identification of critical judgment and technical factors.

Drs Pearlman, Norton, and Stiegmann are obviously distressed that the current conduct of resident training may not impart uniform expertise to trainees who will later practice surgery. They apparently consider the performance of operations such as radical pancreaticoduodenectomy by trainees who will later practice a specialty other than surgery to be misappropriation of educational resources. They further bemoan the fact that a high proportion of graduates of residencies in surgery seek education in other disciplines after their residency. It is worth considering whether availability of experience in complex operative procedures is related to the problem of retention of surgical trainees within the specialty of surgery.

In my opinion, the problem of retention of excellent trainees within the specialty is unrelated to the assignment of the resident to particular services or to the caseload allocation within a residency program. It is more likely that the choice of training has to do with perceived needs for practice location and life-style rather than the availability of operative experience. Furthermore, it seems relevant that we assign the problem of decreasing numbers of "true general surgeons" to its proper place as part of a symptom complex that is representative of an underlying disease process. I believe that the symptom of nonretention is the result of the fragmentation of our specialty at the hands of the people who practice and teach it. The initiatives undertaken recently by leadership organizations such as the American Board of Surgery, the American College of Surgeons, and the American Surgical Association should serve as a remedy. As a program director and practicing surgeon, I join my colleagues from Colorado in pledging my determination to end fragmentation.

Channeling scarce clinical experience to prepare residents to practice surgery seems desirable. The absence of a national consensus among the boards and residency review committees of the various surgical specialties relative to the duration and content of training for individuals seeking to practice specialties such as thoracic, plastic, and pediatric surgery hinders the development of a consistent policy that is fair to all trainees.

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archives of Surgery

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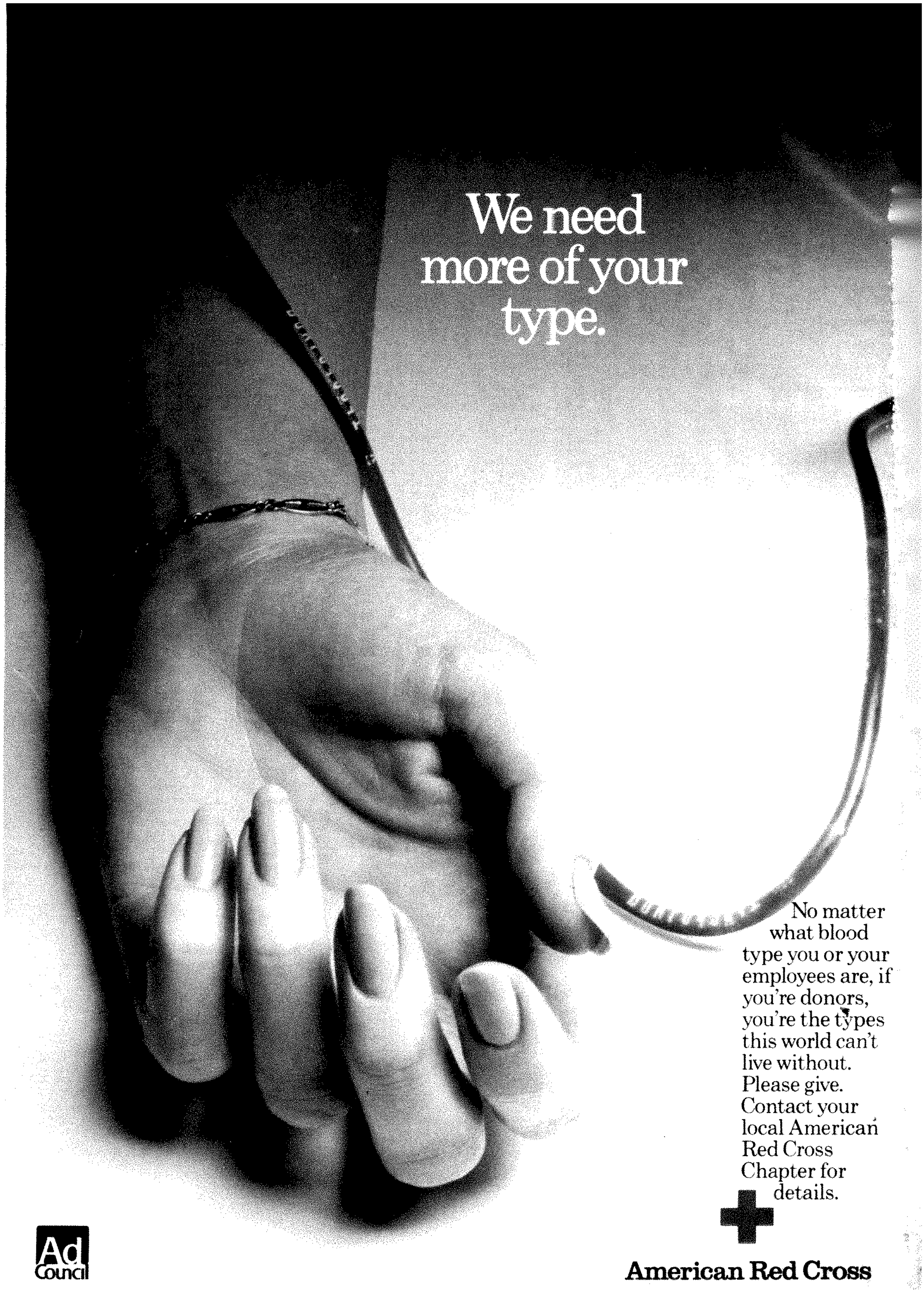
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to carcinoembryonic antigen, and isotype of immunoglobulin by enzyme-linked immunosorbent assay (ELISA) were determined for the supernatant of each visible hybridoma. The reactive clones were subcloned by limiting dilution.[19]

Supernatant of Pokeweed Mitogen–Stimulated T Lymphocytes (sPWM-T)

Human T lymphocytes were prepared from heparinized peripheral blood lymphocytes by the E rosette technique.[20] Briefly, peripheral blood lymphocytes were obtained by Ficoll-Hypaque density gradient centrifugation (Pharmacia, Piscataway, NJ). The lymphocytes were then treated with L-leucine methyl ester, 2.5 mmol/L (Sigma, St Louis, Mo), to reduce inhibitory cells (natural killer–like cells, cytotoxic T lymphocytes, and a subset of $CD8^+$ T cells) for IVI, as described previously.[21] The T helper–enriched preparation was obtained by incubating the L-leucine methyl ester–treated lymphocytes with sheep red blood cells (Cappel, Durham, NC). The sheep red blood cells were then lysed with red blood cell lysing solution (Sigma). A 1:100 dilution of pokeweed mitogen (GIBCO, Grand Island, NY) was added to T cells at a concentration of 4×10^9/L in complete RPMI 1640 supplemented with 10% autologous serum and incubated for 48 hours. The supernatant obtained after centrifugation to remove the pokeweed mitogen–stimulated T cells was designated sPWM-T. Supernatant of mixed lymphocytes culture (sMLC) was prepared by mixing heterologous lymphocytes of two patients at a ratio of 1:1, with a final concentration of 4×10^9/L, and cultured for 72 hours. Both supernatants were stored at −20°C until use.

IVI

Lymphocytes from cancer patients were cultured in complete medium with either 25% sPWM-T or 25% sMLC (vol/vol). Carcinoembryonic antigen (CEA) was used for IVI. Purified CEA at various concentrations was added to the stimulated lymphocytes for a period of 5 to 6 days. At the end of the culture, the viability of the lymphocytes was determined by 0.05% trypan blue exclusion prior to fusion. The mean viability was approximately 70%.

ELISA

Enzyme-linked immunosorbent assay was performed to assess immunoglobulin production and tumor reactivity of hybridomas, as described elsewhere.[22] Briefly, the ELISA plates were prepared by coating the plates with HT-29 or CaCO2 cells at 5×10^4 cells per well. After blocking with phosphate-buffered saline–0.5% bovine serum albumin solution, 50 μL of the testing supernatant was added to each well for 1 to 2 hours at room temperature. After washing, horseradish peroxidase–conjugated goat anti–human immunoglobulin (anti-IgM and anti-IgG were from Jackson, West Grove, Pa, and anti-IgA was from Zymed, San Francisco, Calif) was added for an incubation of 45 minutes. The substrate, orthophenylenediamine, was added for color reaction. The plates were read at 492 nm with a microplate reader (MR 700, Dynatech Laboratories Inc, Chantilly, Va). The background optical density (OD_b) was obtained by substituting phosphate-buffered saline–bovine serum albumin solution for the testing supernatant; it was 0.050 or lower. At the 96-well stage, supernatants with ODs greater than 0.250 were regarded as positive. Subsequently, because few IgM-secreting clones bound nonspecifically to the ELISA plates, new criteria were established to evaluate the ELISA results:

$$\text{Criterion A: } \Delta OD < 1.000 \text{ and } OD_s - OD_f > 0.200, \text{ and}$$
$$\text{Criterion B: } \Delta OD \geqslant 1.000 \text{ and } OD_s - OD_f > 0.150,$$

where $\Delta OD = OD_s - OD_b$, OD_s (sample OD) represents the OD obtained from specific binding of supernatant to the antigen-coated ELISA plates, and OD_f (false OD) represents the OD obtained from nonspecific binding of supernatant to the ELISA plates without antigen coating.

Immunoperoxidase Staining of Colon Cancer Cells

A cytology smear of HT-29 cells or CaCO2 cells was fixed with cold acetone for 10 minutes. Cells were stained by the direct immunoperoxidase method. Horseradish peroxidase–conjugated goat anti–human IgM was used as the secondary antibody. The color was developed with diaminobenzidine (Sigma). The pattern of staining was

Table 1.—Hybridoma Formation by Patients' Lymphocytes From Lymph Nodes With and Without IVI*

	Lymph Node†								
	A1			A2			A3		
	IVI			IVI			IVI		
	sPWM-T	sMLC	Non-IVI	sPWM-T	sMLC	Non-IVI	sPWM-T	sMLC	Non-IVI
No. of clones per 10^7 lymphocytes from lymph nodes	84.3	37.3	18.6	128.6	23.7	15.5	116.7	49.4	3.7
No. of HT-29 tumor-reactive clones/ No. of wells plated (%)	4/80 (5)	0/80	5/480 (1)	8/192 (4.2)	1/192 (0.5)	2/576 (0.3)	6/120 (5)	3/128 (2.3)	1/288 (0.3)
No. of HT-29 tumor-reactive clones per 10^7 lymphocytes from lymph nodes	7.8	0	1.56	6.3	0.74	0.52	7.1	3.53	0.52
No. of stable HT-29 tumor-reactive clones‡	2	0	0	3	1	0	3	0	1
No. of stable CEA-reactive clones‡	1	0	0	1	0	0	0	0	0
Names of stable clones	PA1-1, PA1-2	...	...	PA2-1, PA2-2, PA2-3	MA2-1	...	PA3-1, PA3-2, PA3-3	...	CK2

*IVI indicates in vitro immunization; sPWM-T, supernatant of pokeweed mitogen–stimulated T lymphocytes; sMLC, supernatant of mixed lymphocytes culture; and CEA, carcinoembryonic antigen.

†We used lymphocytes from three lymph nodes of a single patient with colon cancer to generate human monoclonal antibodies by three protocols. The A1 lymph node was closest to and the A3 lymph node was farthest from the main tumor mass.

‡Tumor or CEA reactivity was determined *after* expansion of the clones.

Generation of Human Monoclonal Antibodies Against Colon Cancer

Keiji Koda, MD; Mark C. Glassy, PhD; Helena R. Chang, MD, PhD

• Lymphocytes from regional lymph nodes of patients with colon cancer were fused with a human lymphoblastoid cell line with or without in vitro immunization. The efficacy of these two protocols for the generation of human monoclonal antibodies against colon cancer was investigated. The hyperplastic lymph nodes adjacent to the tumor were the best source of B lymphocytes. Fusion frequency and the number of tumor-reactive clones were markedly increased when the in vitro immunization protocol was applied prior to fusion. As a stimulant in in vitro immunization, the supernatant of pokeweed mitogen–stimulated T lymphocytes was superior to the supernatant of mixed lymphocytes culture. Carcinoembryonic antigen at 20 μg/L seemed to be the optimal dose for in vitro immunization. The reactivities of human monoclonal antibodies thus generated were measured by enzyme-linked immunosorbent assay and confirmed by immunoperoxidase staining. Combining in vitro immunization with lymphocytes of cancer patients may lead to the successful production of clinically useful human monoclonal antibodies.

(*Arch Surg.* 1990;125:1591-1597)

Since the first report of human monoclonal antibody (HuMAb) production using Epstein-Barr virus in 1977 by Steinitz et al,[1] many efforts have been made to generate clinically useful HuMAbs. However, the development of HuMAbs has been limited compared with the development of mouse monoclonal antibodies. This is due primarily to the lack of ideal human fusion partner cells and the lack of effective protocols of immunization to enrich the sensitized B lymphocytes. The production of chimeric HuMAbs with the Fc portion of the mouse monoclonal antibody replaced by human counterparts[2-5] and the production of specific HuMAbs from Epstein-Barr virus transformed lymphocytes[6] have not led to significant changes in the clinical application of HuMAbs. On the other hand, results of efforts to generate HuMAbs with defined specificity by primary in vitro immunization (IVI) of human lymphocytes are encouraging.[7-10]

Human monoclonal antibodies have been produced against tumor-associated antigens by using lymphocytes derived from cancer patients.[11-17] This suggests that cancer patients have tumor-specific B lymphocytes. However, B lymphocytes specific to tumor-associated antigens are extremely few in the natural state. The aim of this study is to improve the yield of HuMAbs reactive to colon cancer. We explored a combined approach with IVI protocols and lymphocytes from cancer patients. The optimal condition of IVI was studied, and the effect of nodal status on the production of tumor-reactive human hybridomas was examined.

MATERIALS AND METHODS

Lymphocytes of Lymph Nodes

Halves of seven lymph nodes of three patients with colon cancer were harvested from fresh colectomy specimens. The remaining halves were submitted for histopathologic study. The lymphocytes were cryopreserved at −70°C until use. The viabilities before and after cryopreservation were approximately 99% and 90%, respectively. Three lymph nodes from each of the two patients used in the study were designated A1, A2, and A3 and B1, B2, and B3. "One" indicated that the lymph node was closest to the main tumor mass and "3" referred to the farthest regional lymph node. One lymph node, harvested from the third patient, was referred to as lymph node C.

Cell Lines

A human B lymphoblastoid cell line derived from parental WIL-2 cells,[18] SHFP-1, was the human fusion partner cell line used in this study. Colon cancer cell lines HT-29 and CaCO2 were obtained from American Type Culture Collection, Rockville, Md. They were cultured in RPMI 1640 medium supplemented with 10% to 20% fetal calf serum.

Fusion and Cloning

The maintenance of SHFP-1 cells and the fusion procedure have been described in detail elsewhere.[18] Briefly, one part of lymphocytes from the lymph nodes and two parts of SHFP-1 cells were fused with 50% polyethylene glycol 1500 (Beringer, Mannheim, Germany). The hybrids were selected by medium containing hypoxanthine, aminopterin, and thymidine (Beringer). Reactivity to HT-29 cells, reactivity

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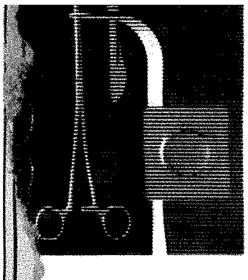
Accepted for publication August 30, 1990.

From the Departments of Surgery, University of California San Diego Medical Center and the Veterans Affairs Medical Center (Drs Koda and Chang), and BioTechnetics (Dr Glassy), San Diego.

Read before the 14th Annual Surgical Symposium of the Association of Veterans Affairs Surgeons, Charleston, SC, May 8, 1990.

Reprint requests to UCSD Medical Center and VAMC, V-112H, 3350 La Jolla Village Dr, San Diego, CA 92161 (Dr Chang).



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In intra-abdominal and gynecologic infection due to indicated organisms

Intravenous or Intramuscular Use
EF SUMMARY

ICATIONS AND USAGE
ATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the wing infections when caused by susceptible strains of the designated organisms:
iary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus abilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia yeri*, and *Morganella morganii*.
er respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *hylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae luding ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*
and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicilse-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* cies (excluding enterococci), and *E coli.*
ecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicilse-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enteroci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, vatus, B thetaiotaomicron*), *usobacterium* species,* and gram-positive anaerobic cocci (including *tococcus* and *Peptostreptococcus* species*).
a-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptoccus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus.**
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other ious infections in which the causative organism has not been identified, it is possible to use CEFOTAN ncomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. e dosage recommended in the labeling of both antibiotics may be given and depends on the severity the infection and the patient's condition.

TE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully nitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is longed, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. hough, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that phrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

ROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain stoperative infections in patients undergoing surgical procedures that are classified as clean conaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transrethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In paents undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping f the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identificaon of the causative organism so that appropriate therapeutic measures may be initiated.

ONTRAINDICATIONS
EFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

ARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of llergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. erious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, paricularly colitis.

NFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

ARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 00 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:}\quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:}\quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

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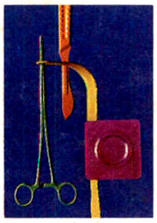

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Please see adjacent page for brief summary of prescribing information.

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